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TADDOL-derived phosphorus ligands in asymmetric catalysis

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References

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Transition metals

Enantioselectivity

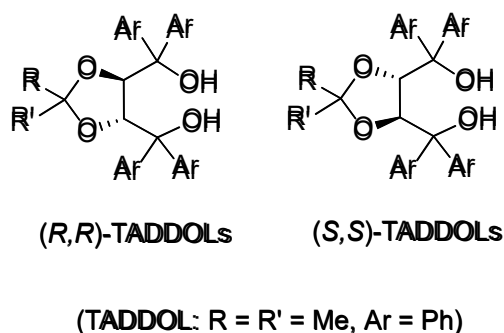
Chirality

Enantioselective transformations

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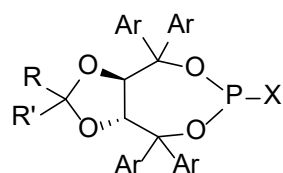
1. Introduction

The success of asymmetric metal catalysis is related to the choice of efficient chiral ligands for achieving enantioinduction [1]. The nature of the ligand, especially its steric and electronic properties, strongly influences both the reactivity of the active metal complex and the level of selectivity provided. The simple access to ligand libraries is essential for the optimization of the reaction. Therefore, ligand scaffolds which are easily modifiable, preferentially at multiple sites, are highly desirable. Actually, the most challenging chiral ligands employed in metal asymmetric catalysis must be readily available, cheap and fine-tunable to allow optimization of enantioselectivity and efficiency. Among them, TADDOL-derived ligands [2], containing two adjacent diarylhydroxymethyl groups in a *trans* relationship on a 1,3-dioxolane ring, arise from the inexpensive chiral source that presents the advantage to be available in both enantiomeric forms (Scheme 1). TADDOL ligands were introduced in 1982 by Seebach et al. as novel chiral backbones for asymmetric synthesis [3]. They are easily prepared from chiral acetals or ketals of tartrate esters by reaction of the latter with aromatic Grignard reagents.



Scheme 1. Structure of TADDOLs.

On the other hand, phosphorus ligands also constitute an important family of chiral ligands, being widely employed in conjunction with transition metals to promote a wide variety of enantioselective transformations [4]. Arisen from the combination of these two types of ligands, TADDOL-derived phosphorus ligands constitute privileged scaffolds in asymmetric synthesis. Among them, the most employed in asymmetric metal catalysis are monodentate phosphoramidites ($X = N$), phosphites ($X = O$) and phosphonites ($X = C$) depicted in Scheme 2. In the last decade, TADDOL-based monophosphoramidite ligands have been the most applied in asymmetric metal catalysis before the corresponding phosphites and the phosphonite ligands. The versatility of TADDOLs and their derivatives stems from the easy variation of the substituents (R , R' , Ar) around the TADDOL framework. In the case of TADDOL-derived phosphorus ligands, the substituent X on the phosphorus atom provides an additional site for modification.

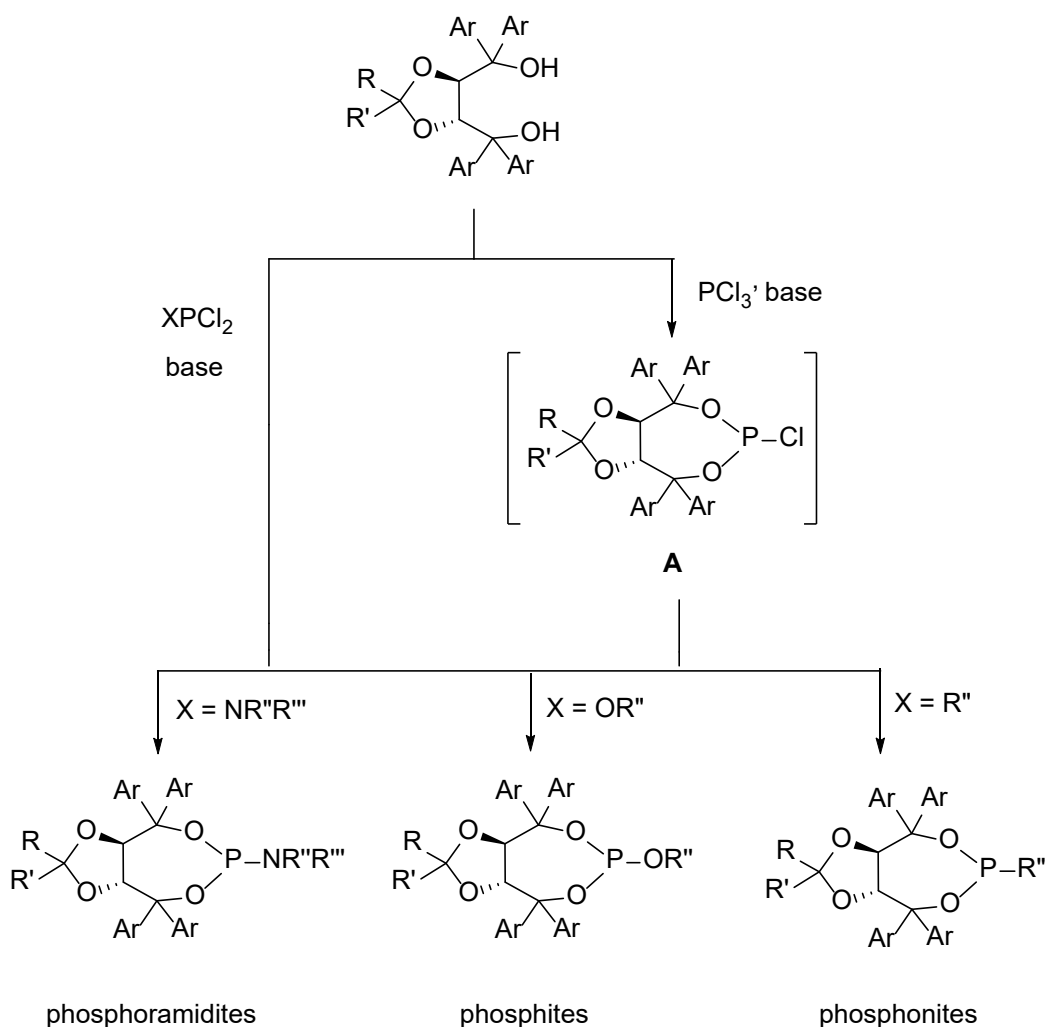


$X = N$: phosphoramidites
 $X = O$: phosphites
 $X = C$: phosphonites

Scheme 2. Structure of monodentate TADDOL-derived phosphorus ligands.

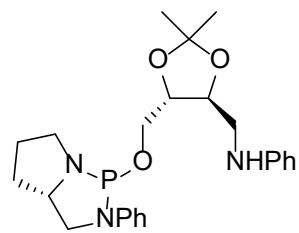
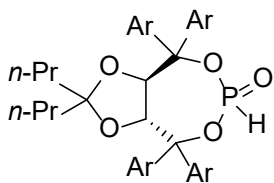
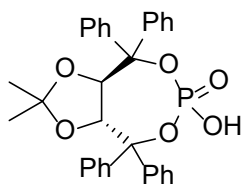
The first synthesis of TADDOL-derived phosphorus ligands was reported by Seebach et al. [5], in 1993. In these studies, several TADDOL-derived phosphonites and phosphites were investigated as chiral ligands in a variety of reactions. The two principal synthetic routes to access TADDOL-based phosphorus ligands, such as phosphoramidites ($X = N$), phosphites (X

= O) and phosphonites ($X = C$), are depicted in Scheme 3. The first and most direct one involves the reaction of TADDOL with Cl_2PX in the presence of a base such as TEA (with $X =$ alkoxy, dialkylamine or alkyl) [6]. The second possibility consists in the initial formation of TADDOL-chlorophosphate **A** from the reaction of TADDOL with PCl_3 followed by nucleophilic substitution with the desired alcohol, amine or carbon based-nucleophile [5,7].

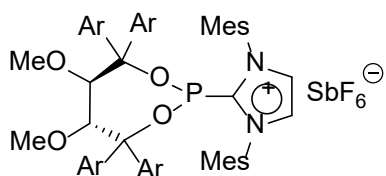


Scheme 3. Synthesis of monodentate TADDOL-derived phosphorus ligands.

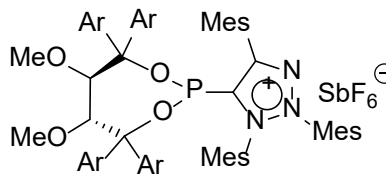
Along with widely employed monodentate TADDOL-derived phosphorus ligands depicted in Scheme 2, other types of phosphorus ligands derived from TADDOL have been successfully applied to promote a variety of enantioselective metal-catalyzed reactions, such as phosphoric acids, biphosphines, biphosphites and diamidophosphites among others (Scheme 4).



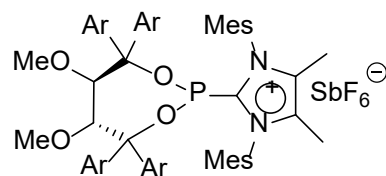
Ar = 2-Naph



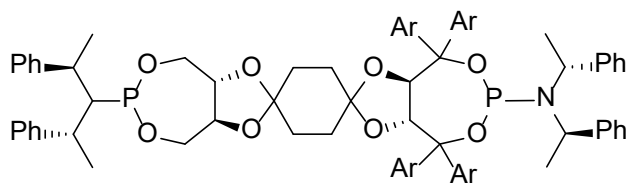
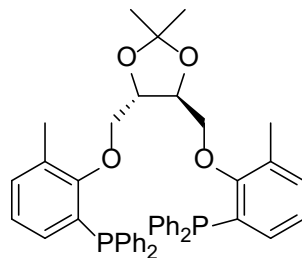
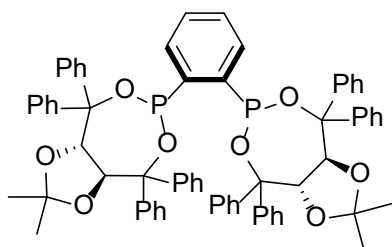
Ar = $p\text{-F}_3\text{CC}_6\text{H}_4$



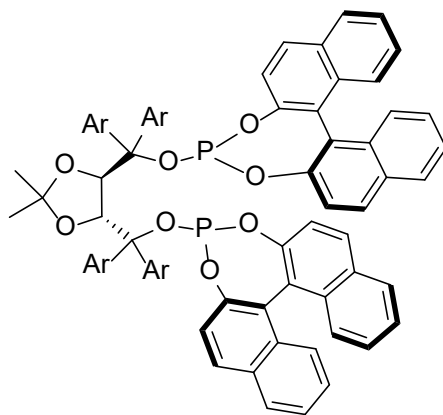
Ar = $p\text{-F}_3\text{CC}_6\text{H}_4$



Ar = $p\text{-F}_3\text{CC}_6\text{H}_4$



Ar = $p\text{-(}t\text{-Bu)C}_6\text{H}_4$



Ar = $p\text{-(}t\text{-Bu)C}_6\text{H}_4$

Scheme 4. Other TADDOL-derived phosphorus ligands.

The goal of this review is to update the field of enantioselective transformations promoted by TADDOL-derived phosphorus ligands published since the beginning of 2011, since this field was most recently reviewed by Lam in 2011, covering the literature up to 2010 [8]. This latter report demonstrated that before 2011 rhodium was probably the most employed metal to be used in asymmetric catalysis in combination with TADDOL-derived phosphorus ligands. Indeed, chiral rhodium catalysts derived from this type of ligands have been densely applied before 2011 to promote a wide variety of enantioselective transformations, spanning from hydrosilylations, hydroborations, diborations, cycloadditions, desymmetrizations of *meso*-epoxides, cyclization of aromatic imines, hydroformylations to reductive aldol reactions. Complexes of palladium also provided excellent enantioselectivities in different types of reactions, such as allylic substitutions, Heck and Suzuki reactions. Moreover, copper catalysts derived from these ligands were successfully employed to promote conjugate additions and allylic substitutions while silver complexes gave good results in cycloadditions, nickel catalysts in nucleophilic allylations, zinc complexes in desymmetrizations of *meso*-epoxides, and platinum catalysts in hydroborations. Along with Lam's report, it must be noted that in 2015, the special field of TADDOL-based phosphorus(III)-ligands in enantioselective Pd(0)-catalysed C–H functionalizations was reviewed by Cramer and Pedroni [9]. Moreover, a chapter on the use of all types of chiral TADDOL derivatives in asymmetric synthesis was published in 2011 [2c]. In a different area, the involvement of TADDOL derivatives as organocatalysts have been the subject of two reviews published in 2013 and 2016 [10]. The present review is divided into seven parts, dealing successively with enantioselective reactions catalyzed by palladium, rhodium, gold, copper, nickel, platinum and other metal complexes derived from chiral TADDOL-based phosphorus ligands. The first part focusing

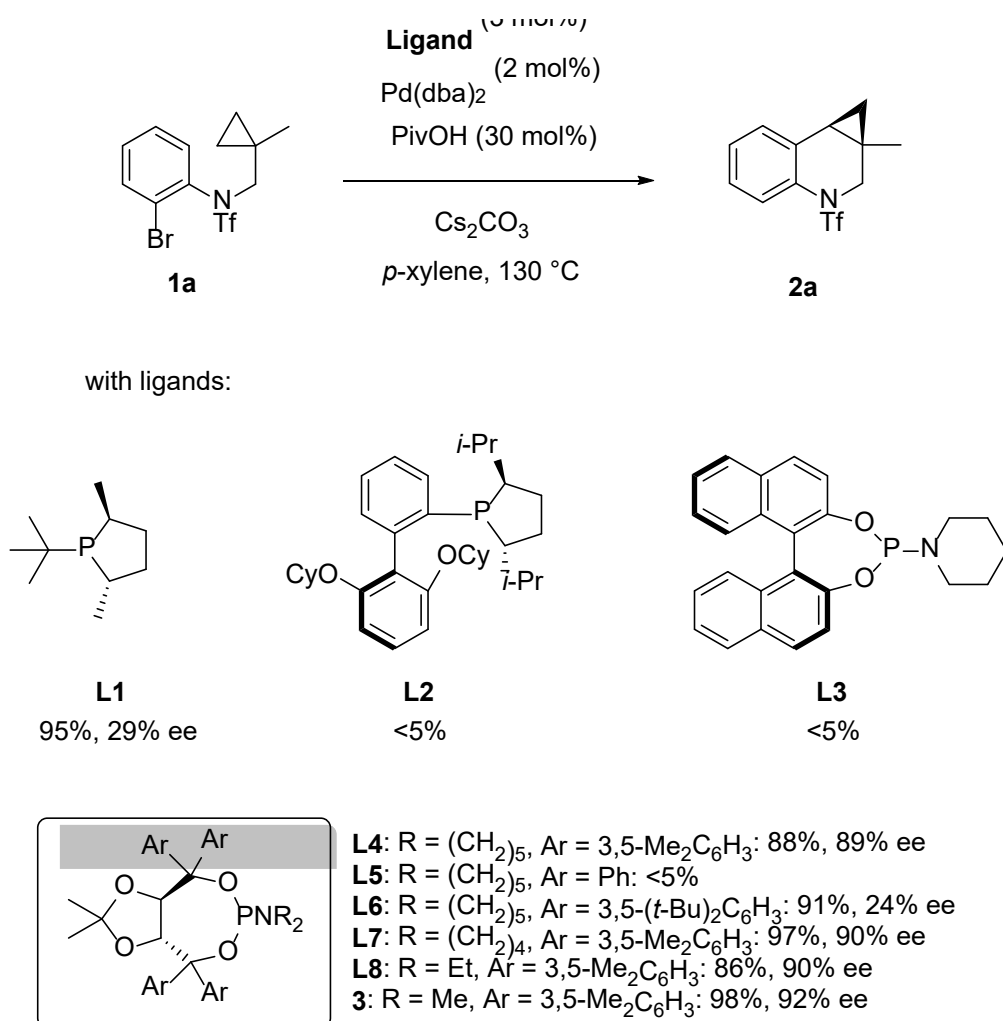
on palladium is subdivided into four sections involving successively C–H functionalizations, cross-couplings, allylations and miscellaneous transformations. The second part dedicated to rhodium complexes is subdivided into three sections, dealing successively with hydroborations, cycloadditions/cyclizations and other reactions. The third part focusses on gold-catalyzed reactions, such as cycloadditions/cyclizations and C–H functionalizations. The fourth part of the review is consecrated to copper catalysis and is subdivided into three sections treating Michael reactions, allylic alkylations and domino/tandem reactions. The fifth part focusses on nickel-catalyzed transformations, such as hydrocyanations and other reactions. The sixth part is dedicated to platinum catalysis with reactions, such as hydrosilylations and diborations. The final part of the review collects a variety of transformations catalyzed by other metals.

2. Enantioselective palladium-catalyzed reactions

2.1. C–H Functionalizations

Palladium complexes of monodentate TADDOL-derived phosphorus ligands have shown excellent performance in a variety of enantioselective reactions, such as Tsuji–Trost [11] and Heck [12] reactions among others [7f,13], and C–H functionalizations introduced in the last fifteen years [9]. The mechanism of the latter transformations was investigated in 2006 by Echavarren et al., showing that these reactions most likely occur via a proton abstraction pathway in which an anionic species coordinated to the metal center effects a C–H bond cleavage by deprotonation with a concomitant C–Pd(II) bond formation [14]. The enantioselective functionalization of C–H bonds catalyzed by chiral transition metal complexes constitutes direct atom- and step-economic regioselective routes to many potential chiral products [15]. A variety of cyclopropyl derivatives have been investigated as potential substrates in asymmetric intramolecular palladium-catalyzed C–H arylations related to the fact that cyclopropanes are found in many natural and bioactive products and are also key and

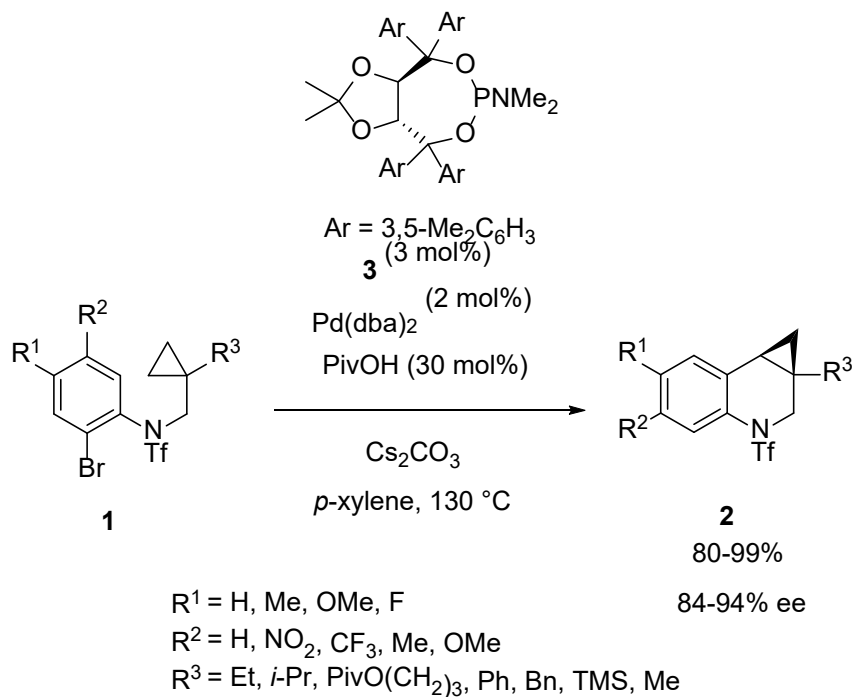
versatile synthetic intermediates for ring-expansion or ring-opening reactions [16]. In contrast to the formation of cyclopropane rings, the direct functionalization of an existing cyclopropyl unit is largely underdeveloped. In this context, Cramer and Saget reported in 2012 an enantioselective intramolecular palladium-catalyzed C–H arylation of unbranched cyclopropylmethyl anilines **1** that resulted in the formation of the corresponding chiral tetrahydroquinolines **2** (Scheme 5) [17]. Several types of chiral ligands were investigated in such reactions, such as chiral and electron-rich monodentate phosphine **L1** which was found to react smoothly (95% yield) albeit with a low enantioselectivity (29% ee). Another electron-rich phosphine ligand **L2** showed a very low reactivity (<5% yield). Then, the authors investigated less-electron-rich phosphoramidites **L3-L8** and **3**. While BINOL-based ligand **L3** did not promote the reaction at all, TADDOL-derived ligands **3**, **L4** and **L6-L8** generally provided excellent yields (86-98%) and low to very high ee values (24-92% ee). The nature of the aromatic substituent on the TADDOL backbone (Ar) was found to play a critical role in both the reactivity and enantioselectivity of the reaction. Whereas the reactivity was very low (<5% yield) with simple phenyl groups (Ar = Ph in ligand **L5**), bulky 3,5-di-*tert*-butylphenyl groups (Ar = 3,5-(*t*-Bu)₂C₆H₃) in ligand **L6** were found detrimental to the enantioselectivity (24% ee). Actually, both high yields and enantioselectivities were achieved with ligands **L7-L8** bearing 3,5-xyllyl substituents (Ar = 3,5-Me₂C₆H₃) with the best compromise (98% yield, 92% ee) when combined with a dimethylamino group (R = Me) as in optimal ligand **3**.



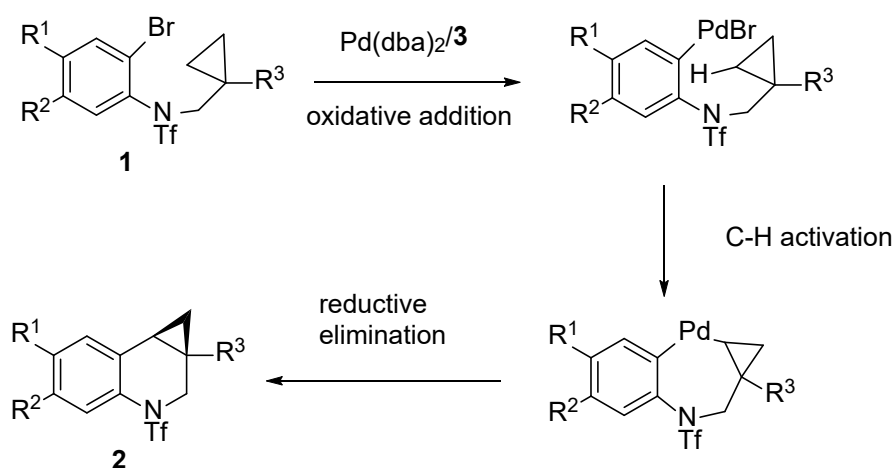
Scheme 5. Investigation of ligands in C–H arylation of cyclopropylmethyl aniline **1a** [17].

Indeed, the use of optimal ligand **3** allowed chiral tetrahydroquinolines **2** to be synthesized in both high yields (80-99%) and enantioselectivities (84-94% ee). As presented in Scheme 6, the reaction proceeded with a low catalyst loading as low as 2 mol% of Pd(dba)₂ combined with 3 mol% of chiral TADDOL-derived phosphoramidite ligand **3**. The process required the use of a carboxylic acid, such as pivalic acid, as an additive and was performed at 130 °C in *p*-xylene as the solvent. Uniformly excellent results were achieved with (functionalized) aliphatic as well as aromatic substituted cyclopropanes. Moreover, the aromatic ring could exhibit both *meta*- and *para*-substituents with respect to the bromine atom. This simple and novel methodology allowed a direct access to the core of tetrahydroquinolines, which is widely present in many natural and biologically active products [18]. A possible mechanism is proposed in Scheme 6 involving palladium oxidative addition followed by C–H activation to

give a seven-membered palladium intermediate which finally afforded the product through reductive elimination.

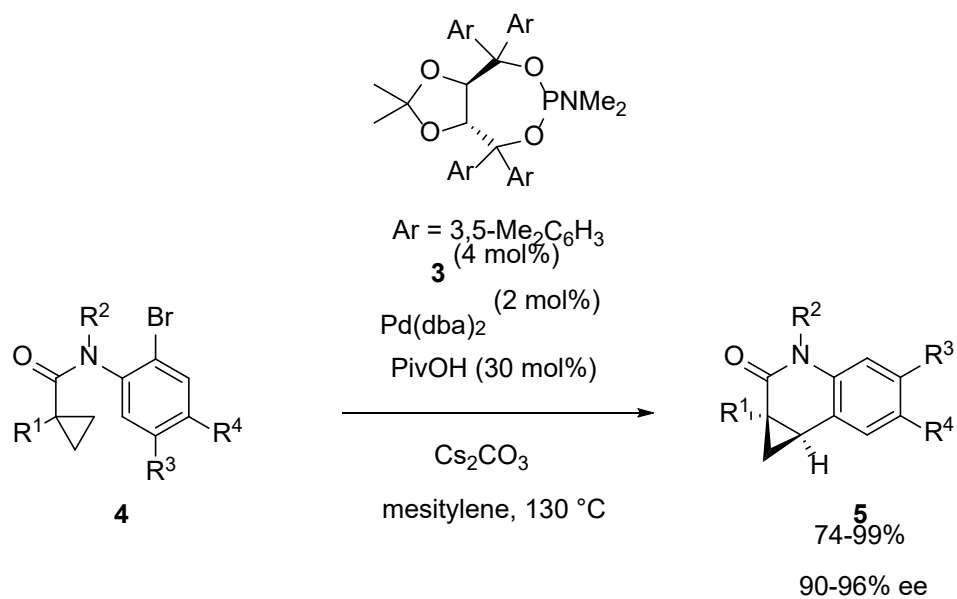


proposed mechanism:



Scheme 6. C–H Arylation of cyclopropylmethyl anilines [17].

In 2015, other substituted cyclopropanes with different linkers, such as cyclopropyl acetamides **4**, were also submitted by the same authors to comparable intramolecular asymmetric C–H arylation under closely related conditions [19]. In this case, the optimal conditions were achieved by using 4 mol% of the same chiral ligand **3** combined with 2 mol% of the same precatalyst in mesitylene at 130 °C (Scheme 7). In the presence of pivalic acid as an additive, the process afforded the corresponding chiral dihydroquinolones **5** in both uniformly high yields (74-99%) and ee values (90-96% ee). Remarkably, an activation of the C(sp²)-H group of the *para*-methoxyphenyl group (R² = *p*-MeOC₆H₄CH₂) could also proceed through a seven-membered palladacycle **B** instead of seven-membered palladacycle **C**, leading to the product arisen from a cyclopropane C(sp³)-H activation. However, the formation of product **6** was not observed and the preference for the cyclopropane C(sp³)-H activation could be explained by a conformational bias of the amide tether.



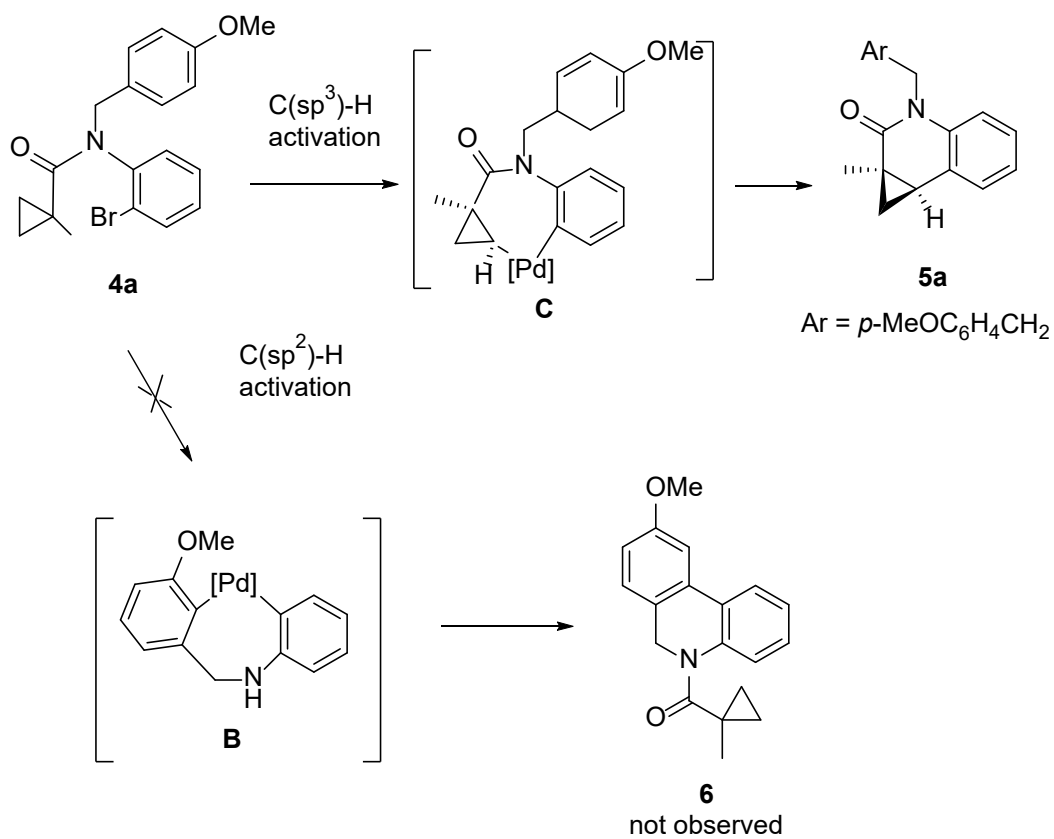
$\text{R}^1 = \text{Bn, Ph, Me}$

$\text{R}^2 = \text{Me, Et, Pr, } p\text{-MeOC}_6\text{H}_4\text{CH}_2, o\text{-MeOC}_6\text{H}_4\text{CH}_2$

$\text{R}^3 = \text{H, Me, CF}_3$

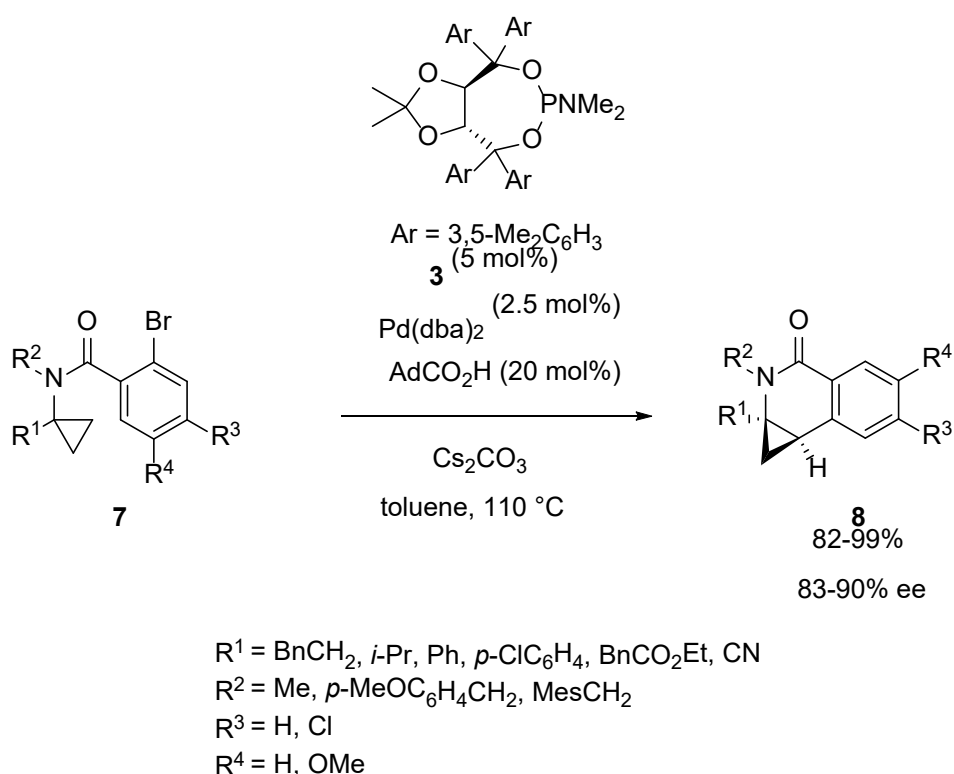
$\text{R}^4 = \text{H, Me, OCF}_3, \text{Cl}$

mechanism (with $\text{R}^1 = \text{Me, R}_2 = p\text{-MeOC}_6\text{H}_4\text{CH}_2, \text{R}^3 = \text{R}_4 = \text{H}$):



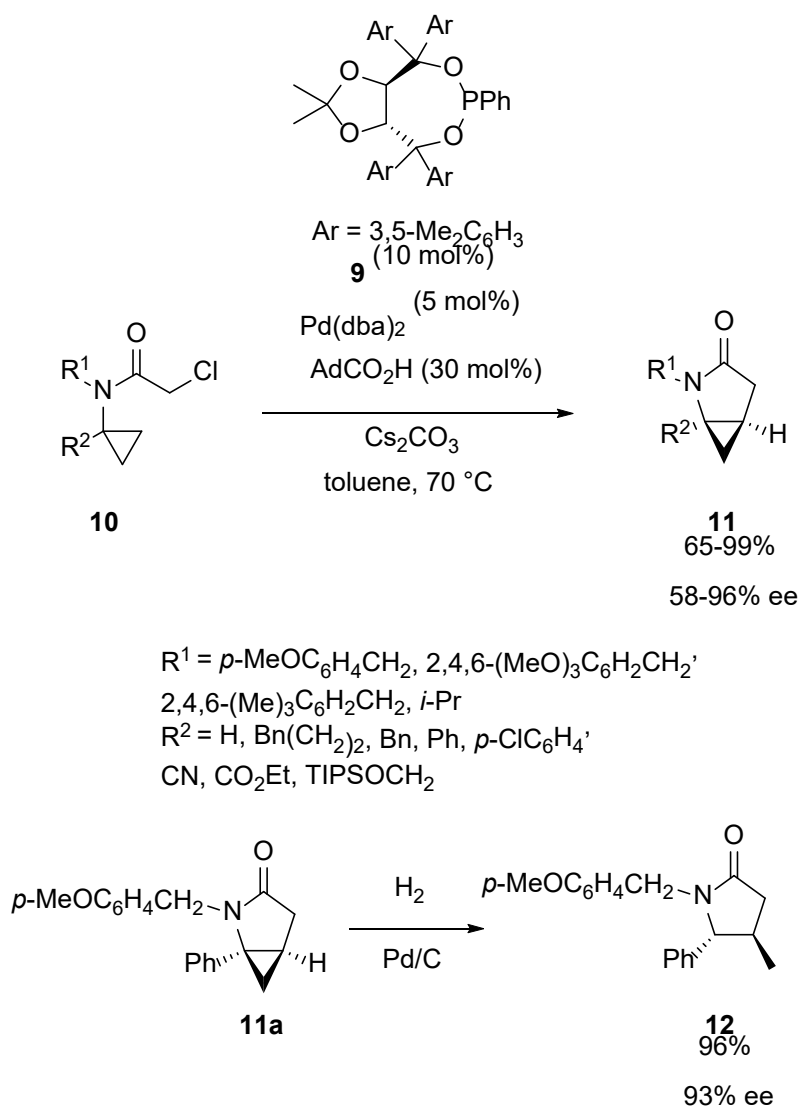
Scheme 7. C–H Arylation of cyclopropyl acetamides [19].

Closely related reaction conditions were also applied to the asymmetric C–H arylation of *N*-cyclopropyl acetamides **7** [19]. In this case, the optimal conditions were based on the use of 5 mol% of the same chiral ligand **3** combined with 2.5 mol% of the same precatalyst in toluene at 110 °C. In the presence of adamantyl carboxylic acid as an additive, the process afforded the corresponding chiral dihydroisoquinolones **8** in uniformly high yields (82-99%) and enantioselectivities (83-90% ee), as shown in Scheme 8. Especially, the catalyst system showed a wide tolerance for the cyclopropane substituent (R^1) which could be linear alkyl, branched alkyl, aryl or benzyl groups as well as ethyl ester or nitrile. The utility of this methodology was shown by its application to develop an efficient asymmetric construction of the seven-membered ring of the cyclopropyl indolobenzazepine core of BMS-791325 (daclatasvir), which is a NS5A inhibitor and that of NS3/4A protease inhibitor asunaprevir.



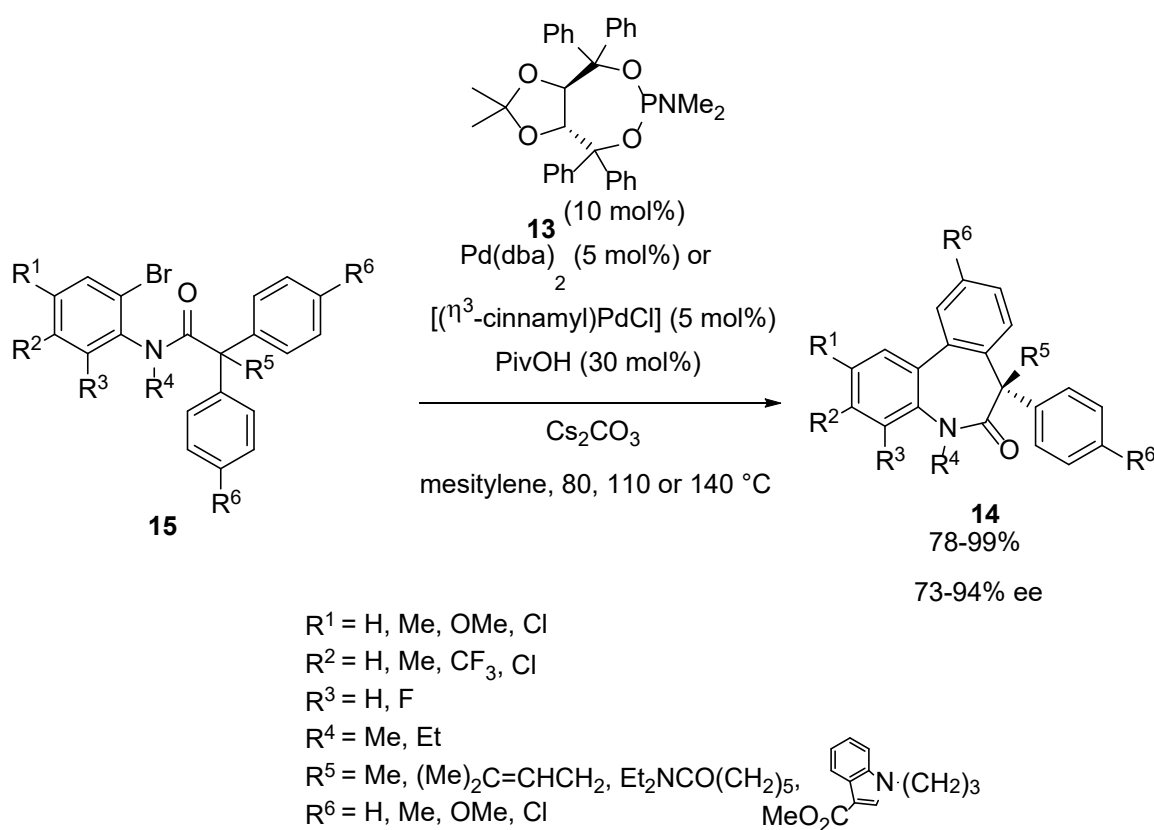
Scheme 8. C–H Arylation of *N*-cyclopropyl acetamides [19].

In the same year, these authors also reported the use of a TADDOL-derived chiral phosphonite ligand **9** to promote an enantioselective palladium-catalyzed C–H functionalization of readily accessible *N*-cyclopropyl chloroacetamides **10** to form chiral γ -lactams **11** with azabicyclo[3.1.0]-hexane scaffolds [20]. The ligand was employed at 10 mol% of catalyst loading in combination with 5 mol% of Pd(dba)₂ as precatalyst in toluene at 70 °C. In the presence of adamantyl carboxylic acid as an additive, the reaction led to chiral bicyclic products **11** in good to excellent yields (65-99%) and enantioselectivities (58-96% ee), as illustrated in Scheme 9. As an application, the cyclopropyl ring of product **11a** (R¹ = *p*-MeOC₆H₄CH₂, R² = Ph) was opened under hydrogenation conditions to form stereospecifically chiral β,γ -disubstituted- γ -lactam **12** in 96% yield and 93% ee.



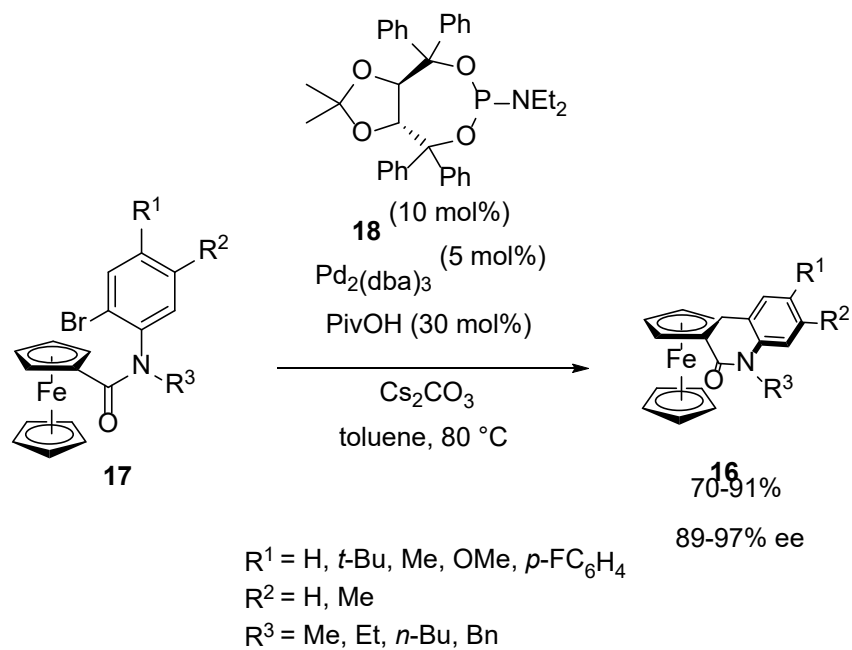
Scheme 9. C–H Arylation of *N*-cyclopropyl chloroacetamides [20].

Earlier in 2013, the same group employed chiral phosphoramidite ligand **13** at 10 mol% of catalyst loading in combination with 5 mol% of Pd(dba)₂ or [(η³-cinnamyl)PdCl] in some cases of substrates to promote the synthesis of chiral dibenzazepinones **14** exhibiting a quaternary stereogenic center through a novel enantioselective intramolecular palladium-catalyzed enantioselective C–H arylation of the corresponding aryl bromides **15** (Scheme 10) [21]. The authors showed that increasing the size of the ligand resulted in decreasing both reactivity and enantioselectivity, thus leading to select ligand **13** as optimal one. The catalyst system was compatible with variously substituted arenes, including halogenated ones. The products were synthesized in both good to high yields (78-99%) and enantioselectivities (73-94% ee).

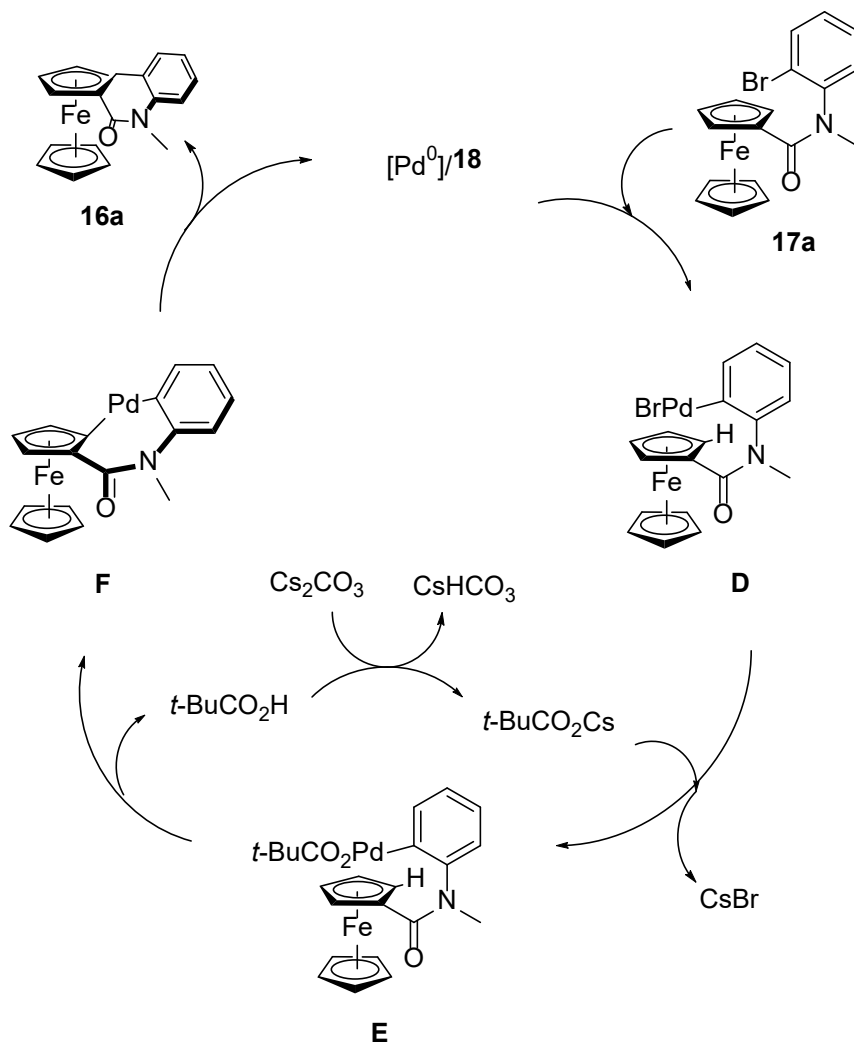


Scheme 10. C–H Arylation of aryl bromides [21].

In 2014, Liu and Zhao disclosed a synthesis of quinolinone-fused planar chiral ferrocenes **16** based on an intramolecular C–H arylation of the corresponding *N*-(2-bromoaryl)ferrocenecarboxamides **17** (Scheme 11) [22]. Performed in the presence of 5 mol% of Pd₂(dba)₃, 10 mol% of chiral TADDOL-derived phosphoramidite ligand **18** and 30 mol% of pivalic acid in toluene at 80 °C, the C–H arylation of a series of *N*-(2-bromoaryl)ferrocenecarboxamides **17** (X = Br) provided the corresponding quinolinone-fused planar chiral ferrocenes **16** in uniformly high yields (70-91%) and enantioselectivities (89-97% ee). In general, substrates bearing larger substituents (R³ = *n*-Bu, Et) at the nitrogen atom provided higher ee values than methyl-substituted ones (R³ = Me). In addition to aryl bromides, an aryl iodide (X = I) was found suitable, leading to the corresponding product with 80% yield and 82% ee whereas aryl chlorides were unreactive. A mechanism is proposed in Scheme 11, beginning with the oxidative addition of the C(sp²)–Br bond onto palladium(0) that provided arylpalladium bromide intermediate **D**. Then, a pivalate anion replaced the bromide ligand on palladium to generate palladium pivalate intermediate **E**. Subsequently, a C–H bond on the cyclopentadienyl ring was cleaved to generate the di(organyl)palladium species **F**. Finally, a reductive elimination furnished the product along with the regeneration of the palladium(0) species.

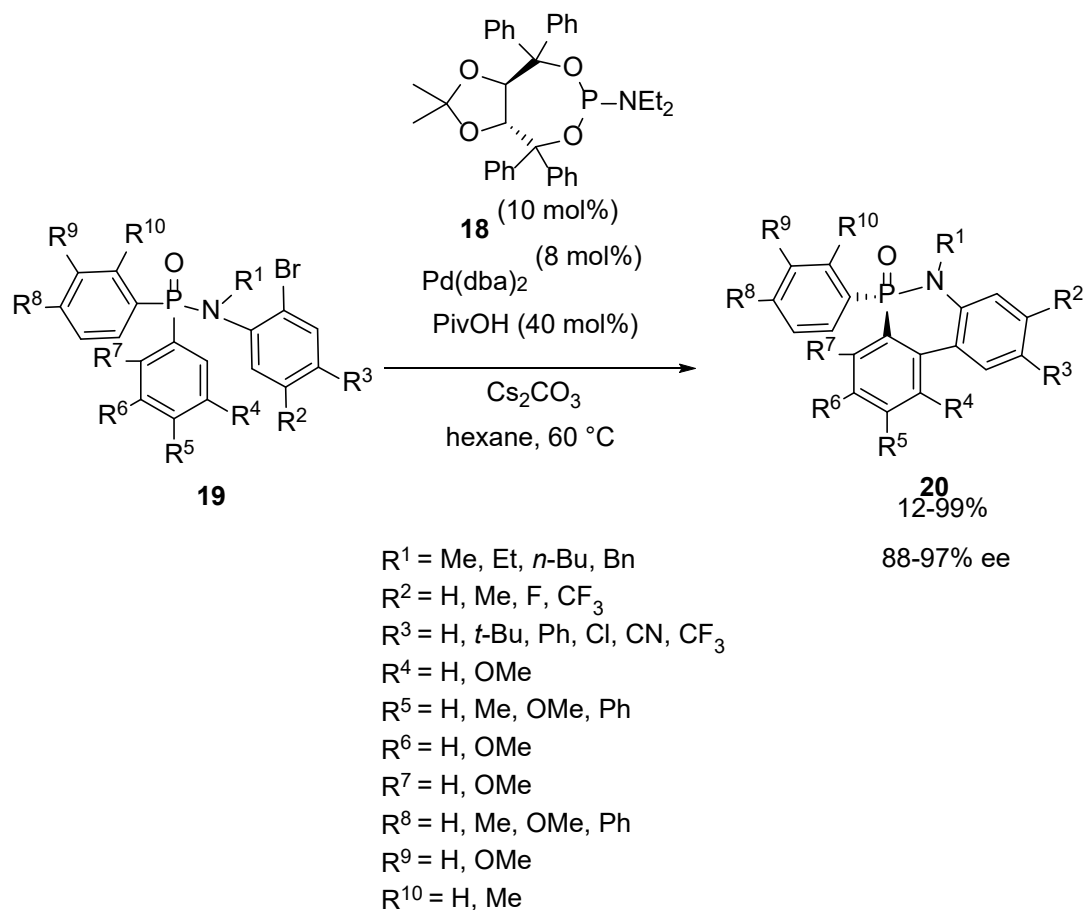


proposed mechanism (with $\text{R}^1 = \text{R}^2 = \text{H}, \text{R}^3 = \text{Me}$):



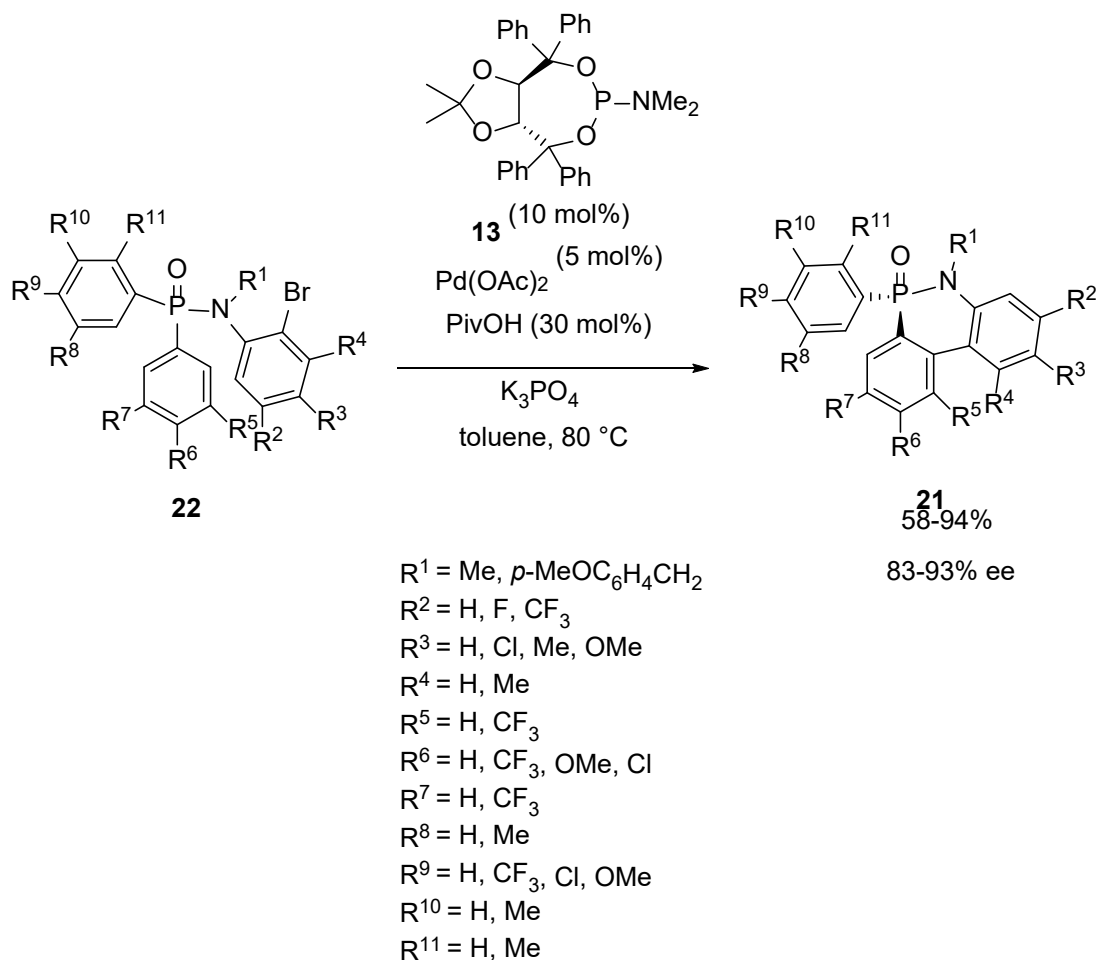
Scheme 11. C–H Arylation of *N*-(2-bromoaryl)ferrocenecarboxamides [22].

In addition to the creation of C-stereogenic centers, C–H arylation can be used to access P-stereogenic compounds. For example, the groups of Liu and Duan independently reported in 2015 a C–H arylation strategy for the asymmetric synthesis of cyclic phosphinic amides. In both cases TADDOL-based phosphoramidites were identified as the most selective ligands while common chiral biaryl phosphines, such as BINAP, led to poor results (5% ee). Therefore, in the study from Liu and Ma, the enantioselective palladium-catalyzed C–H arylation of *N*-(2-bromoaryl)-*P,P*-diphenylphosphinic amides **19** was promoted by a chiral catalyst in situ generated from 8 mol% of Pd(dba)₂ and 10 mol% of chiral phosphoramidite **18** [23]. As presented in Scheme 12, these substrates reacted intramolecularly at 60 °C in the presence of 40 mol% of pivalic acid as an additive in hexane as solvent to afford the corresponding P-chiral cyclic phosphinic amides **20** in low to quantitative yields (12-99%) and uniformly excellent enantioselectivities (88-97% ee). Substrates with bulkier *N*-protecting groups than methyl furnished the desired cyclic products in good yields albeit with lower enantioselectivities. On the other hand, a *N*-benzyl substituted substrate (R¹ = Bn) reacted highly enantioselectively (92% ee) albeit with a low yield (12%).



Scheme 12. C–H Arylation of *N*-(2-bromoaryl)-*P,P*-diphenylphosphinic amides [23].

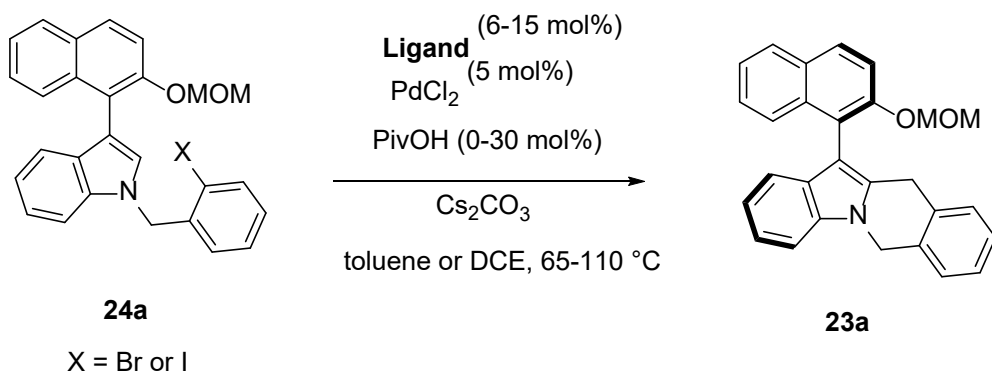
As mentioned above, these reactions were also investigated by Duan et al. by using a closely related chiral ligand **13** at the same catalyst loading (10 mol%) albeit combined with 5 mol% of $\text{Pd}(\text{OAc})_2$ as another precatalyst (Scheme 13) [24]. In this case, the reaction occurred at 80 °C in toluene as the solvent with 30 mol% of pivalic acid as the additive, thus providing *P*-chiral cyclic phosphinic amides **21** with good yields (58-94%) and comparable ee values (83-93% ee) from the corresponding *N*-(2-bromoaryl)-*P,P*-diphenylphosphinic amides **22**.



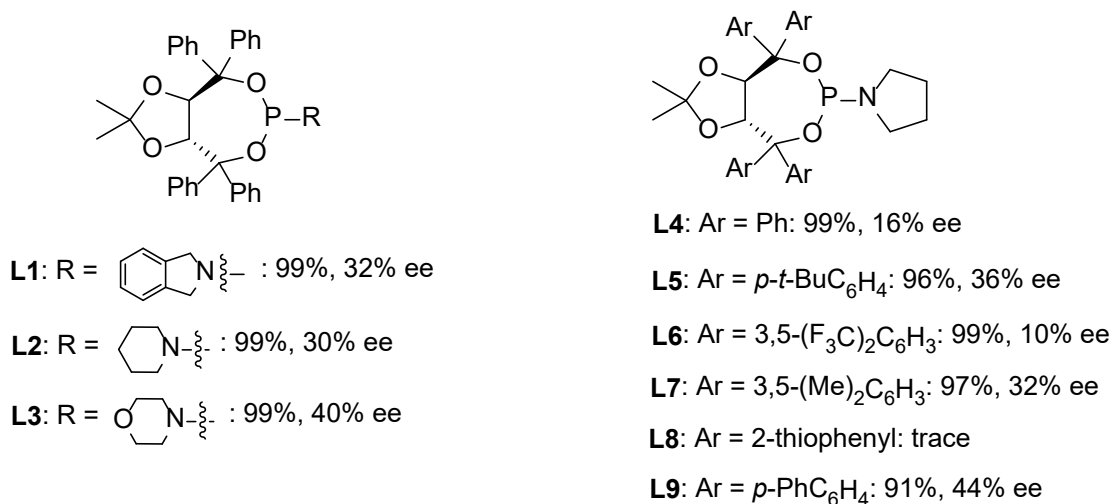
Scheme 13. C–H Arylation of *N*-(2-bromoaryl)-*P,P*-diphenylphosphinic amides [24].

Indoles are important subunits in medicinal chemistry. Consequently, their preparation has attracted much attention from organic chemists. However, the synthesis of naturally occurring atropisomers bearing an indole subunit remains underdeveloped. To fill this gap, Gu et al. developed in 2017 a synthesis of indole-based atropisomers **23** on the basis of an enantioselective palladium-catalyzed intramolecular C–H cyclization of the corresponding indoles **24** [25]. In a first time, BINAP, MOP, phosphoramidites, and DIOP chiral ligands among others were investigated in these reactions, albeit all provided the corresponding products with very low ee values ($\leq 5\%$ ee). Then, a series of TADDOL-based phosphoramidite ligands, including ligands **L1-L4** bearing phenyl substituents (Ar = Ph) and various amine moieties, were synthesized and tested in the cyclization of bromide **24a** but low to moderate ee values (16-40% ee) were obtained for the corresponding product **23a** (Scheme 14). Then, variation in the aryl groups of the TADDOL moiety was investigated, showing that

electron-withdrawing substituents on the aryl groups in ligands **L5-L9** imparted negative effects on the enantioselectivity (0-44% ee). Moreover, when the aryl group was a 2-thiophenyl group in ligand **L8**, only trace amount of the product was formed. However, introducing a biphenyl group (Ar = *p*-PhC₆H₄) into ligand **L9** improved the enantioselectivity to 44% ee. Finally, 1-phenylpiperazine-based phosphoramidite ligand **25** was found optimal ligand since the reaction of iodide **24a** afforded the product with 84% ee before further optimization. Supplementary modifications of the piperazine structure in ligands **L10-L12** proved to be fruitless (70-80% ee).



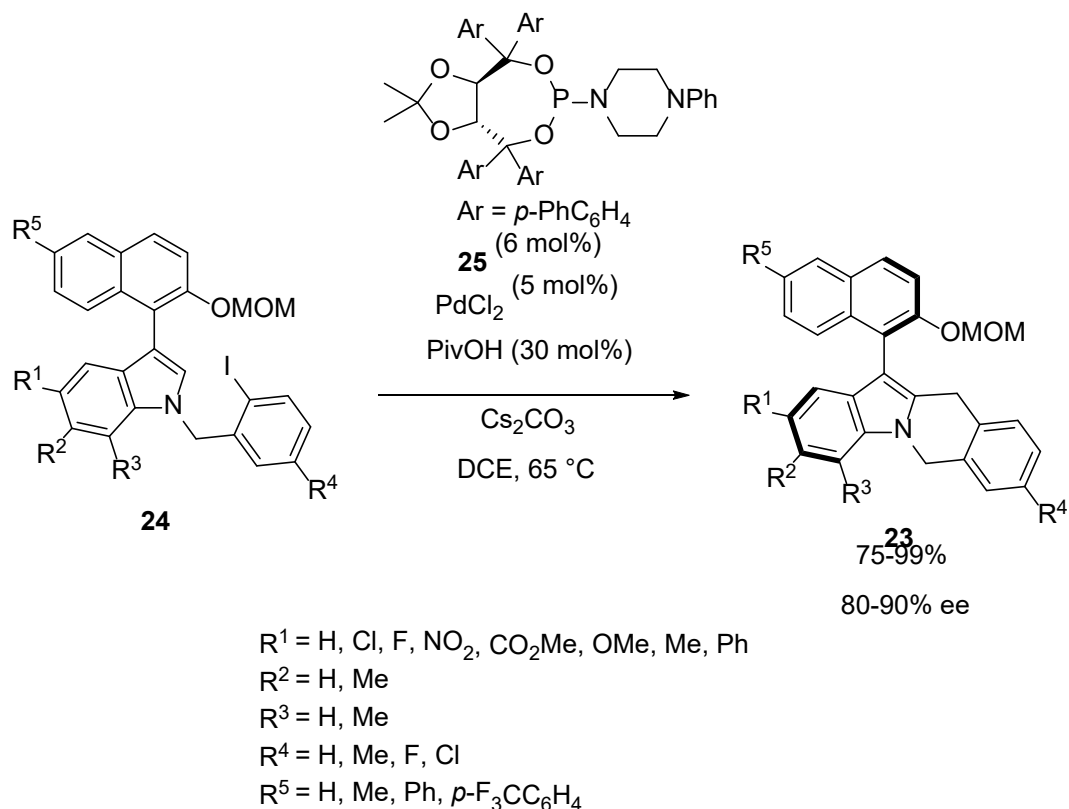
investigation of ligands:



Scheme 14. Investigation of ligands in C–H arylation of indoles [25].

Having selected ligand **25** as optimal and after further optimization of the reaction conditions, the best results were obtained by using 5 mol% of PdCl₂ combined with 6 mol%

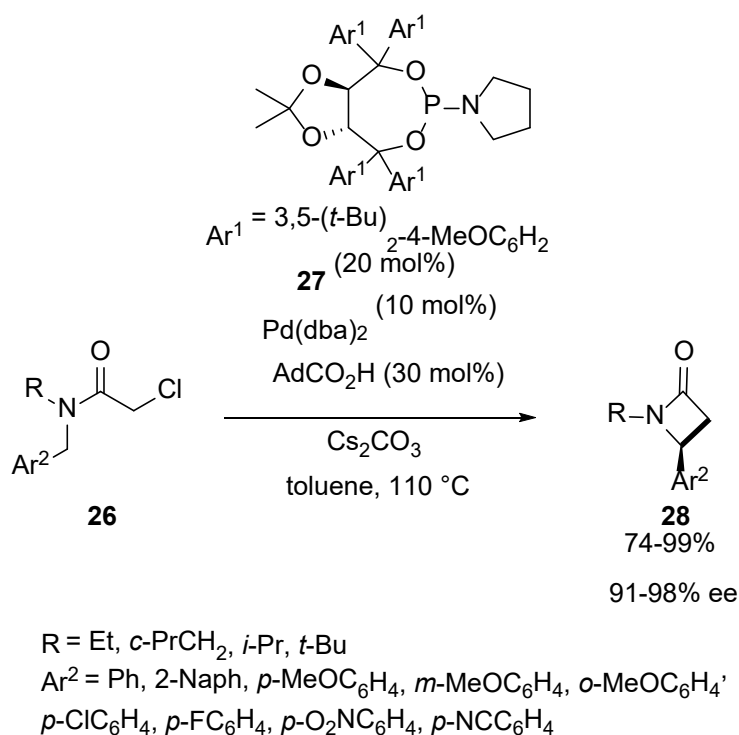
of this ligand **25** in the presence of pivalic acid as an additive (Scheme 15). Performed at 65 °C in DCE as the solvent, the C–H arylation of iodides **24** led to a range of variously substituted indole-based atropisomers **23** with both high yields (75-99%) and enantioselectivities (80-90% ee). These good results were independent of the nature of the substituents exhibited by either the naphthalenol or indole moiety.



Scheme 15. C–H Arylation of indoles [25].

Along with asymmetric C–H arylations, chiral palladium complexes of TADDOL-derived phosphorus ligands have also been applied to promote enantioselective C–H alkylations. This strategy was employed in 2014 by Cramer et al. to develop a novel synthesis of β -lactams, constituting very important structural motifs related to their broad biological activities as well as their propensity to undergo ring-opening reactions. As shown in Scheme 16, this was achieved through an asymmetric C–H functionalization of readily accessible chloroacetamides **26** [26]. This reaction was promoted by a chiral palladium catalyst in situ generated from 10 mol% of Pd(dba)₂ and 20 mol% of bulky chiral phosphoramidite **27**. In the

presence of adamantyl carboxylic acid as the additive in toluene at 110 °C, a range of chloroacetamides **26** underwent an intramolecular asymmetric C–H alkylation, resulting in the formation of the corresponding chiral β -lactams **28** in uniformly both high yields (74-99%) and enantioselectivities (91-98% ee).

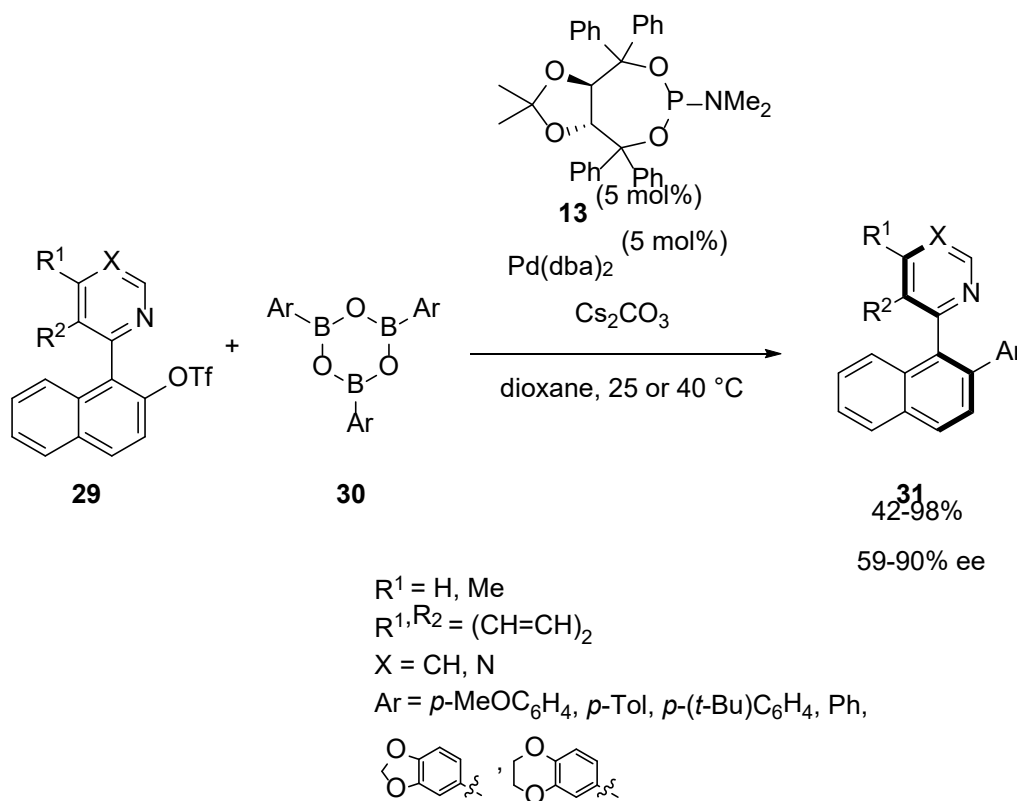


Scheme 16. C–H Alkylation of chloroacetamides [26].

2.2. Cross-coupling reactions

Enantioselective transition-metal-catalyzed cross-coupling reactions are more and more applied in the synthesis of important chiral products [27]. Reactivity and selectivity remain the challenging issues in the field of cross-coupling. Many types of novel chiral ligands and catalysts have been designed to achieve high stereoselectivity in these reactions. Among them are chiral TADDOL-derived phosphorus ligands which play a major role in this field. The transition-metal-catalyzed asymmetric C(sp²)–C(sp²) cross-coupling reaction is one of most efficient methods for constructing biaryl skeletons with axial chirality, which exist in

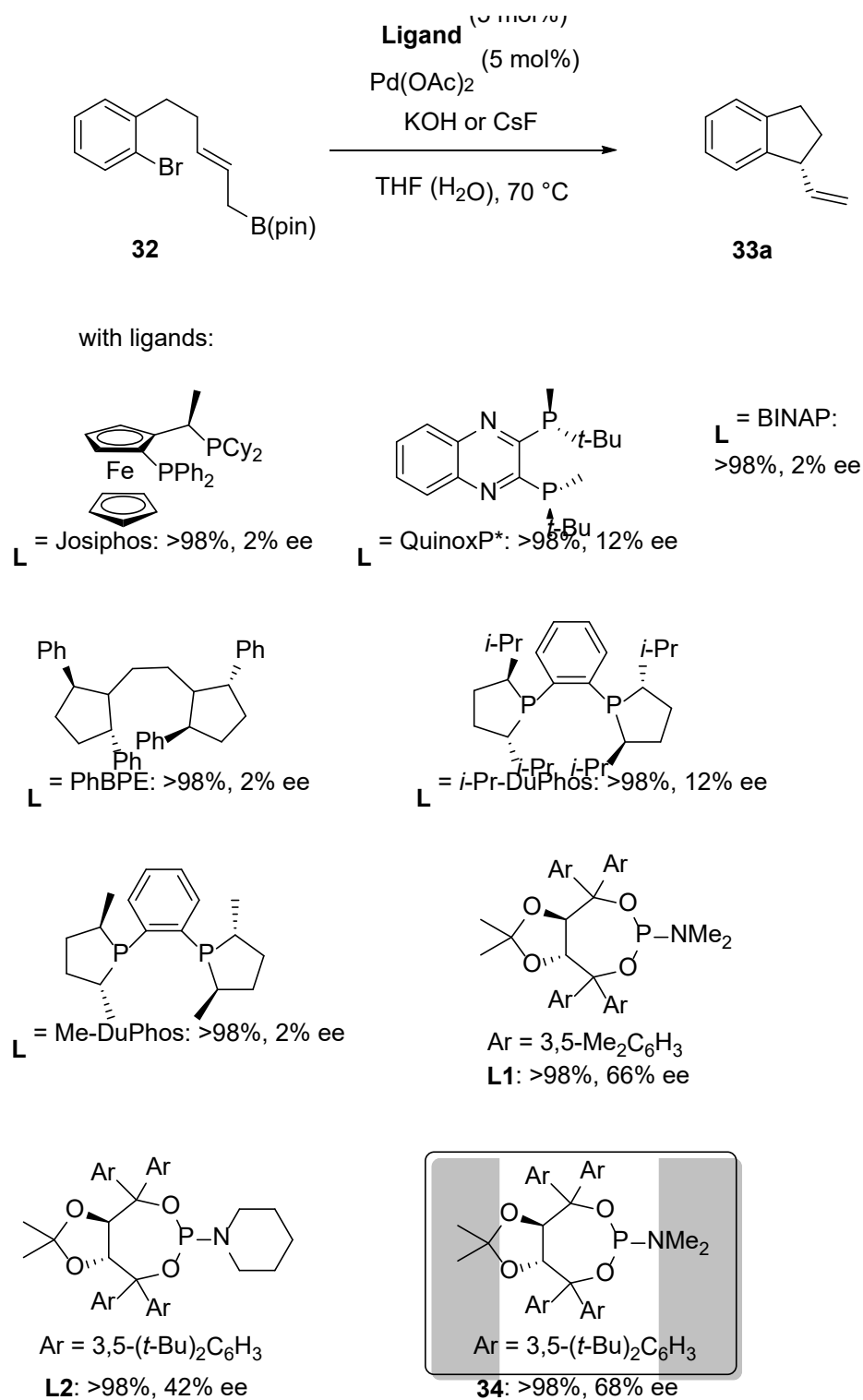
numerous natural products and drugs. In 2013, Lassaletta and Fernandez described an asymmetric synthesis of 2'-substituted 2-aryl pyridines/isoquinolines and related heterobiaryl compounds based on the enantioselective palladium-catalyzed cross-coupling reaction of racemic 2-triflates **29** with aryl boroxines **30** (Scheme 17) [28]. The process employed 5 mol% of a chiral palladium catalyst in situ generated from Pd(dba)₂ and chiral phosphoramidite **13** in dioxane at 25 or 40 °C. Under these conditions, a wide variety of 2'-substituted 2-aryl isoquinolines (R¹,R² = (CH=CH)₂, X = CH) and related heterobiaryls (R¹ = H, R² = Me, X = CH and R¹,R² = (CH=CH)₂, X = N) **29** reacted with different aryl boroxines **30** to give the corresponding axially chiral heterobiaryl products **31** with moderate to quantitative yields (42-98%) and enantioselectivities (59-90% ee), as presented in Scheme 17.



Scheme 17. Coupling of 2'-substituted 2-aryl pyridines/isoquinolines and related heterobiaryls with aryl boroxines [28].

In 2014, Morken and co-workers reported a rare example of intramolecular enantioselective cross-coupling reaction between allyl boronates and aryl halides (Scheme 18) [29]. In a first

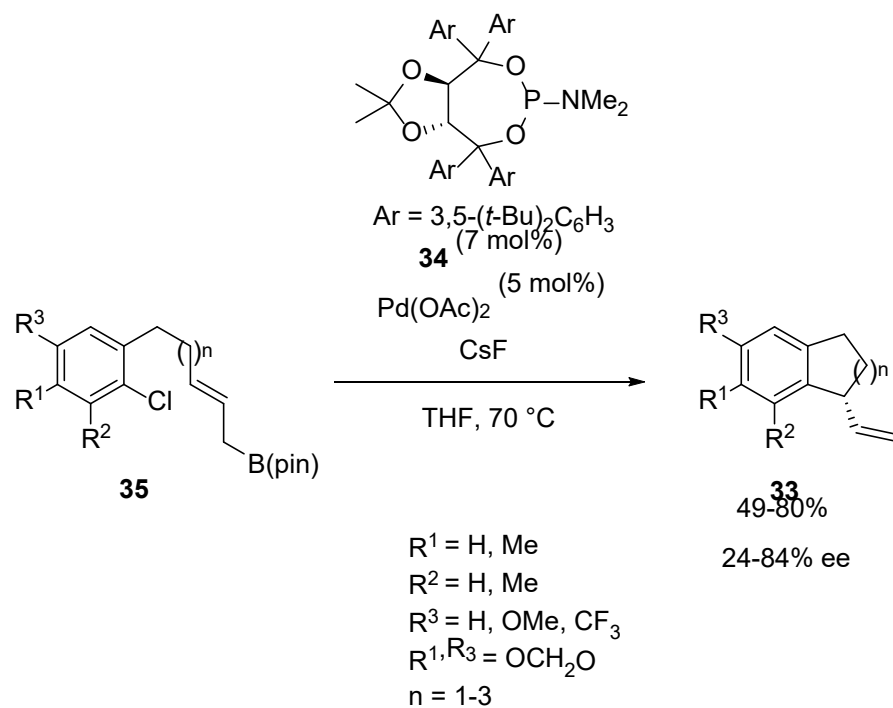
time, various types of chiral ligands were investigated in the asymmetric intramolecular coupling of allyl boronates with aryl bromide **32** to give the corresponding cyclized product **33a** (Scheme 18). A catalyst loading of 5 mol% of a chiral ligand in combination with the same quantity of Pd(OAc)₂ as precatalyst were used at 70 °C in THF(/H₂O) as solvent and in the presence of CsF or KOH as an additive. The use of a variety of bidentate chiral phosphine ligands, such as Josiphos, QuinoxP*, BINAP, PhBPE, *i*-Pr-DuPos and Me-DuPhos, generally resulted in quantitative conversion into the corresponding carbocyclic product **33a** albeit with low levels of enantioselectivity (2-14% ee). Significantly higher enantioselectivities (42-68% ee) were obtained by using monodentate chiral TADDOL-derived phosphoramidite ligands **34** and **L1-L2**. While increasing the size of aryl groups in the ligand resulted in only marginally increased enantioselectivities, it was found that the nature of the amino group was more critical, with small groups yielding superior ee values (68% ee with **34** vs 42% ee with **L2**); which led to select ligand **34** as optimal one.



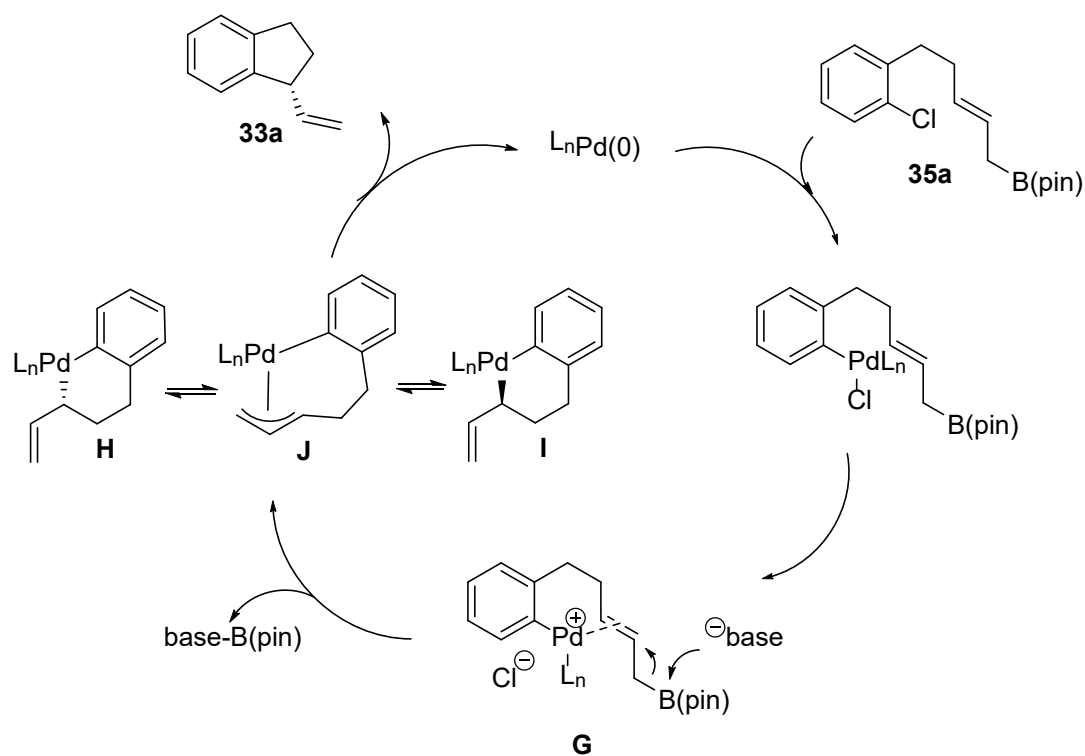
Scheme 18. Investigation of ligands in intramolecular coupling of allyl boronate **32** with aryl bromide [29].

The optimal conditions for the asymmetric intramolecular coupling of allyl boronates with aryl chlorides **35** involved 5 mol% of Pd(OAc)₂ combined with 7 mol% of optimal chiral

phosphoramidite ligand **34** in THF at 70 °C (Scheme 19). Performed in the presence CsF as a base, the allyl–aryl coupling reaction allowed the regioselective formation of chiral carbocyclic products **33** in variable enantioselectivities (24-84% ee) and moderate to high yields (49-80%) starting from the corresponding aryl electrophiles **35** containing a tethered allylboronate. The catalyst system was compatible with the synthesis of five, six and seven-membered carbocyclic products as single regioisomers. The lowest ee value (24% ee) was obtained in the formation of a seven-membered cycle. To explain their results, the authors proposed the mechanism depicted in Scheme 19, beginning with the formation of intermediate **G** arisen from the olefin binding. Then, the latter led to π -allyl palladacycle intermediate **J** through transmetalation. Intermediate **J** could equilibrate into intermediates **H** and **I**. Finally, reductive elimination of intermediates **H**, **I** or **J** led to the product.

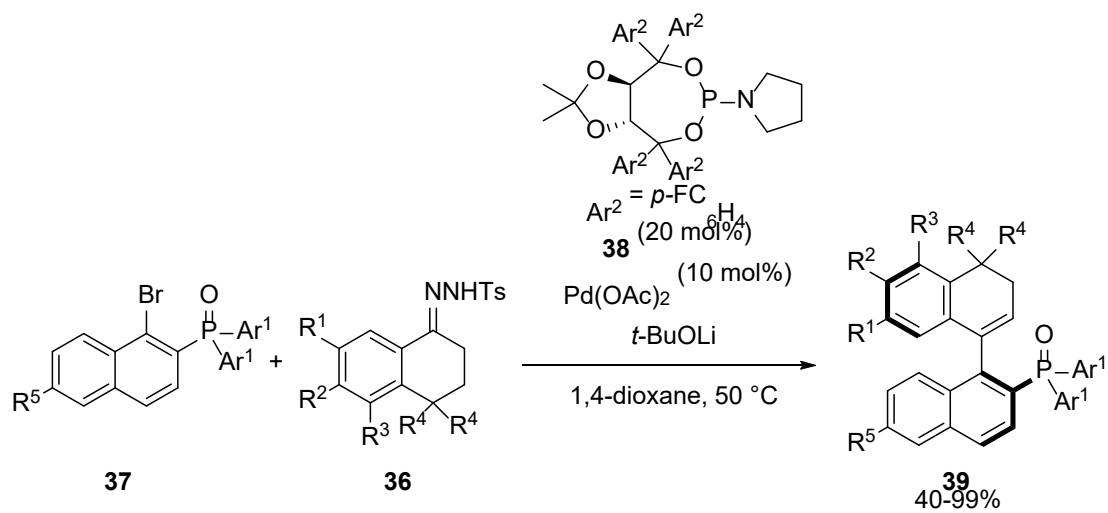


proposed mechanism (with $R^1 = R^2 = R_3 = \text{H}$, $n = 1$):



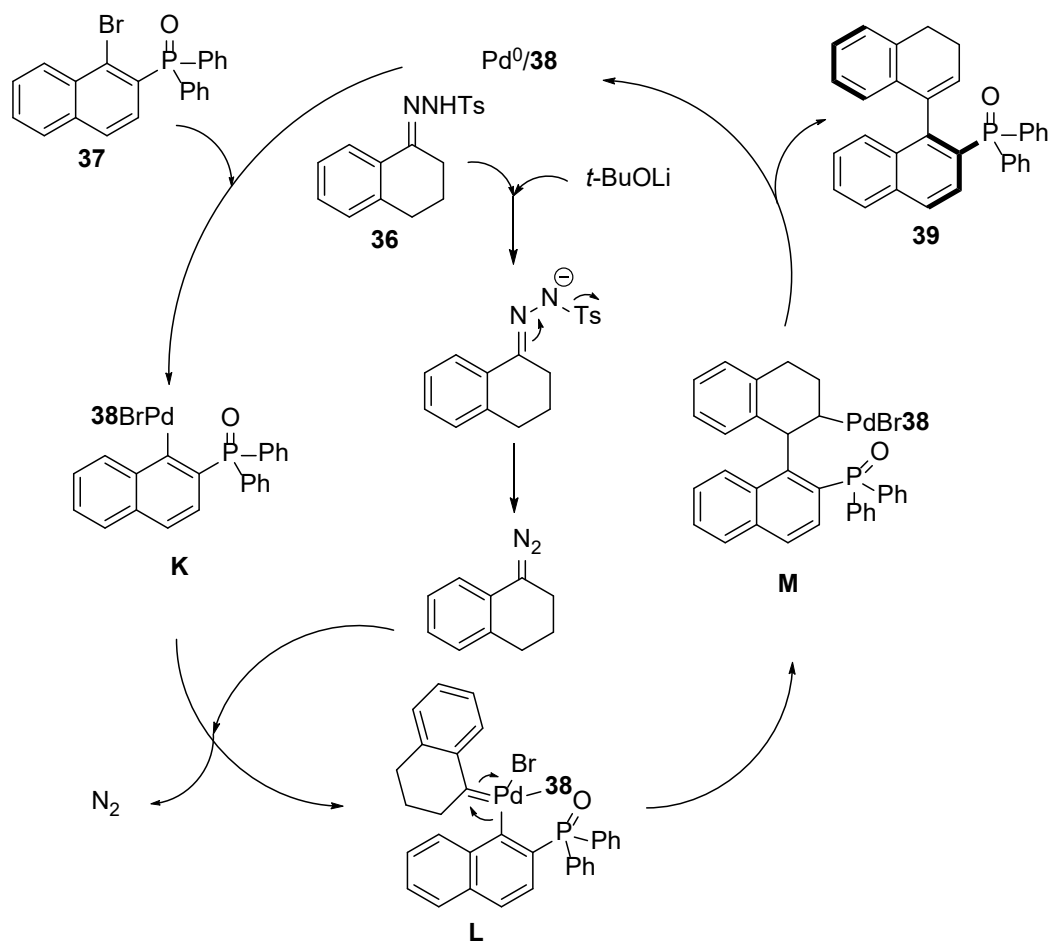
Scheme 19. Intramolecular coupling of allyl boronates with aryl chlorides [29].

A direct way to synthesize axially chiral biaryl compounds is the coupling of two arenes through cross-coupling. An example was described in 2016 by Gu et al. with an enantioselective palladium-catalyzed cross-coupling between hydrazones **36** and aryl bromides **37** (Scheme 20) [30]. Indeed, this process performed in the presence of 10 mol% of Pd(OAc)₂ combined with 20 mol% of chiral phosphoramidite ligand **38** as catalyst system with *t*-BuOLi as base in THF at 50 °C allowed a range of axially chiral 1-vinylnaphthalen-2-yl phosphine oxides **39** to be synthesized in moderate to quantitative yields (40-99%) and uniformly high enantioselectivities (85-97% ee). The reaction conditions were compatible with variously substituted diaryl phosphine oxides as well as tetralone-derived hydrazones, providing comparable results regardless the nature of the substituents. The reaction involved the formation of carbenes as coupling partners, as shown in the mechanism depicted in Scheme 20, beginning with the oxidative addition of Pd(0) with the aryl bromide to give intermediate **K**. Then, the latter reacted with the diazo compound (generated in situ from the hydrazone in the presence of *t*-BuOLi) to afford the carbene-coordinated complex **L**. Subsequently, migration/insertion of **L** furnished a quaternary carbon center bearing a C–Pd bond, and delivered the final product through β-hydride elimination. The origin of the enantioselectivity could partially be affected by the π–π interaction of the phenyl ring of the phosphine oxide with the tetrahydronaphthalene moiety in either intermediates **L** or **M**, since a control reaction with a diethyl phosphonate (OEt instead of Ar¹) as a substrate gave the corresponding product with only 7% ee.



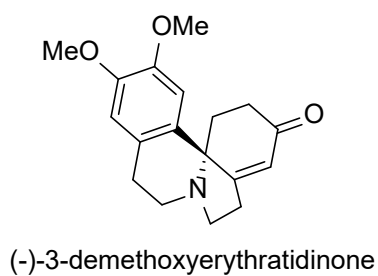
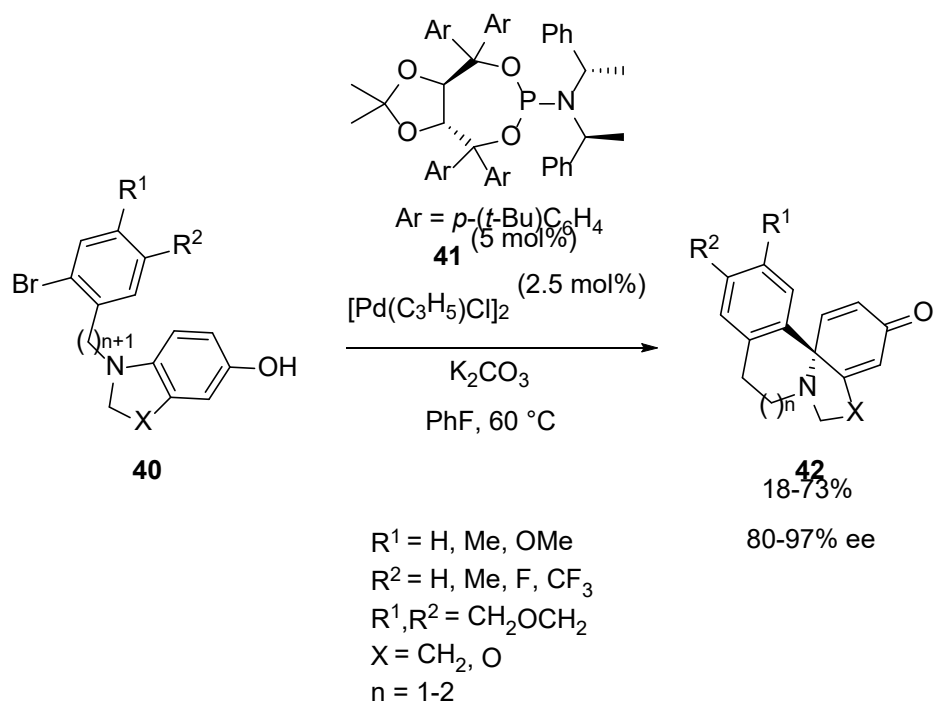
$\text{Ar}^1 = \text{Ph}, p\text{-MeOC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, p\text{-PhC}_6\text{H}_4, p\text{-Tol},$
 $p\text{-FC}_6\text{H}_4, m\text{-MeOC}_6\text{H}_4, m\text{-Tol}, 3,4\text{-F}_2\text{C}_6\text{H}_3'$
 $3,5\text{-Me}_2\text{C}_6\text{H}_3, 1\text{-Naph}, 2\text{-Naph}$
 $\text{R}^1 = \text{H}, \text{F}, \text{Cl}$
 $\text{R}^2 = \text{H}, \text{F}, \text{Cl}, \text{OMe}$
 $\text{R}^3 = \text{H}, \text{OMe}$
 $\text{R}^4 = \text{H}, \text{OMe}$
 $\text{R}^4, \text{R}^4 = (\text{CH}_2)_4$
 $\text{R}^5 = \text{H}, \text{CO}_2i\text{-Pr}$

proposed mechanism (with $\text{R}^1 = \text{R}_2 = \text{R}_3 = \text{R}_4 = \text{R}_5 = \text{H}, \text{Ar}_1 = \text{Ph}$):

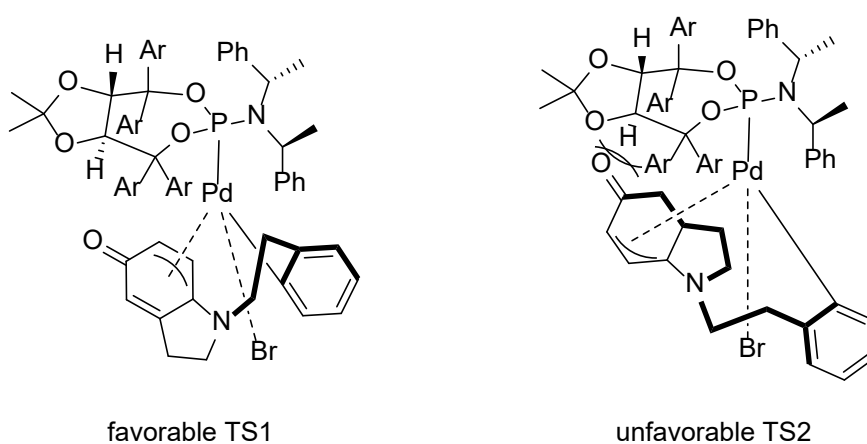


Scheme 20. Coupling of hydrazones with aryl bromides [30].

With the aim of opening a novel route to the erythrinane skeleton, You et al. reported in 2020 an enantioselective palladium-catalyzed intramolecular arylation dearomatization of *para*-aminophenols **40** (Scheme 21) [31]. The coupling reaction occurred at 60 °C in fluorobenzene as the solvent upon catalysis with 2.5 mol% of [Pd(C₃H₅)Cl]₂ and 5 mol% of bulky monodentate chiral TADDOL-derived phosphoramidite **41**, thus delivering the corresponding chiral tetracyclic spiroamines **42** in low to good yields (18-73%) combined with generally high enantioselectivities (80-97% ee). A wide range of 5-hydroxyindoline-derived aryl bromides **40** bearing both electron-donating and electron-withdrawing groups were compatible, leading to the desired products with high ee values (80-97% ee) and moderate to good yields (44-73%). Interestingly, the reaction of substrates bearing tetrahydroquinoline and benzomorpholine scaffolds also provided the corresponding products with good yields (40-66%) and high enantioselectivities (83-97% ee). However, the lowest yield (18%) was obtained in the reaction of a substrate with an elongated tether (n = 2) but combined with 91% ee. The utility of this methodology was demonstrated in a concise total synthesis of naturally occurring biologically active (-)-3-demethoxyerythratidinone. To explain the stereoselectivity of the process, the authors proposed the transition states depicted in Scheme 21. In the favorable transition state TS1, the stereochemistry of the reaction is determined when the phenoxide ring attacked the tricoordinated Pd center ligated with the bulky monodentate chiral phosphoramidite ligand, displacing the Br anion. On the other hand, a stronger steric congestion between the *para*-aminophenoxide ring and the bulky ligand is shown in the unfavorable transition state TS2.

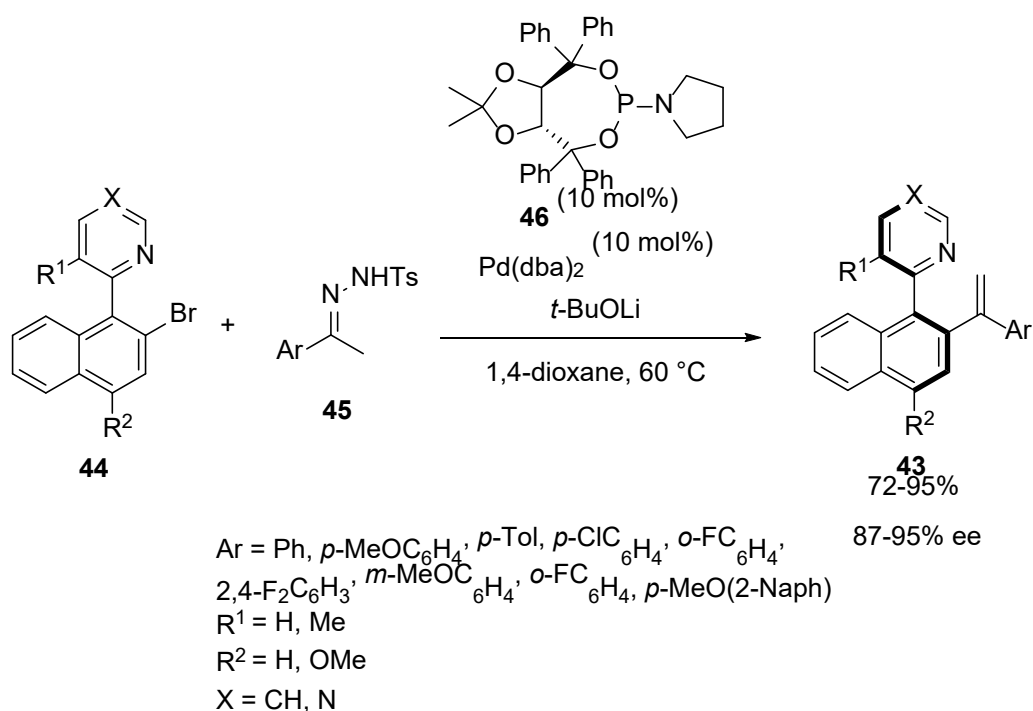


proposed transition states (with $\text{R}^1 = \text{R}_2 = \text{H}$, $n = 1$, $\text{X} = \text{CH}_2$):

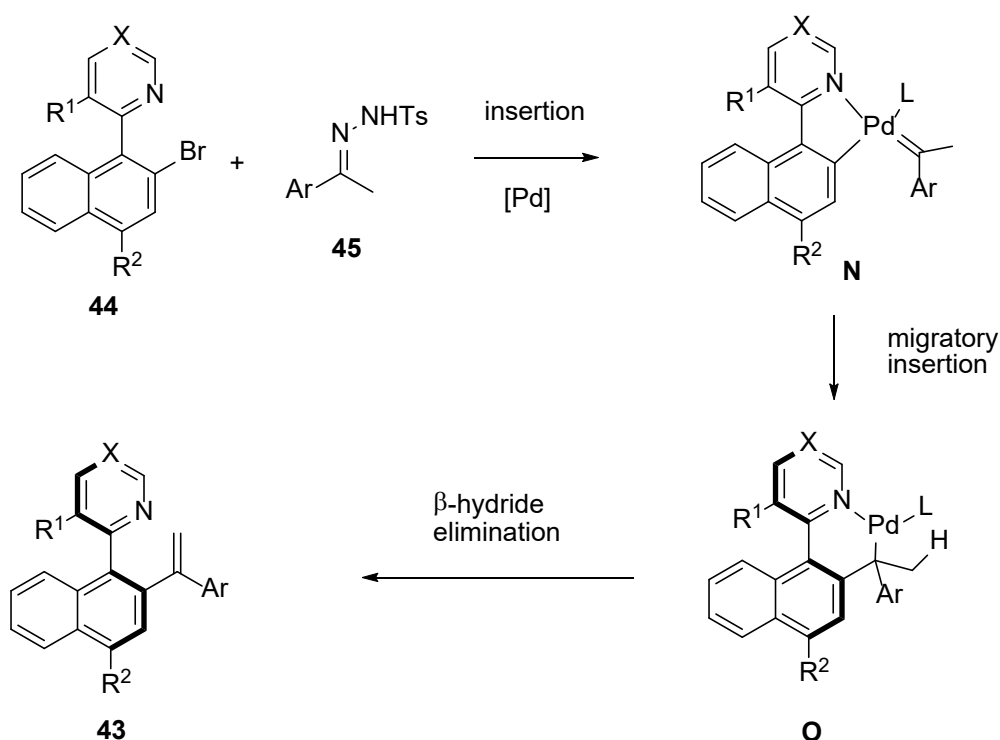


Scheme 21. Intramolecular arylation dearomatization of *para*-aminophenols [31].

In 2022, Lassaletta and Fernandez disclosed a novel synthesis of axially chiral heterobiaryl styrenes **43** based on a dynamic kinetic asymmetric palladium-catalyzed cross-coupling reaction between readily racemic heterobiaryl bromides **44** and *N*-tosyl hydrazones **45** (Scheme 22) [32]. The reaction was promoted at 60 °C in 1,4-dioxane as solvent by a chiral palladium catalyst in situ generated from 10 mol% of Pd(dba)₂ and the same quantity of TADDOL-derived chiral phosphoramidite ligand **46**, thus forming the corresponding axially chiral heterobiaryl derivatives **43** in both uniformly high yields (72-95%) and enantioselectivities (87-95% ee) which demonstrated the high functional group tolerance of the catalyst system. The process was assumed to proceed through palladium/carbene insertion to give labile intermediate **N**, followed by a migratory insertion providing stable intermediate **O** which was finally submitted to β-hydride elimination process to deliver the final product (Scheme 22).



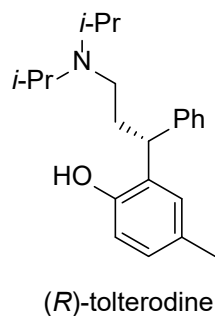
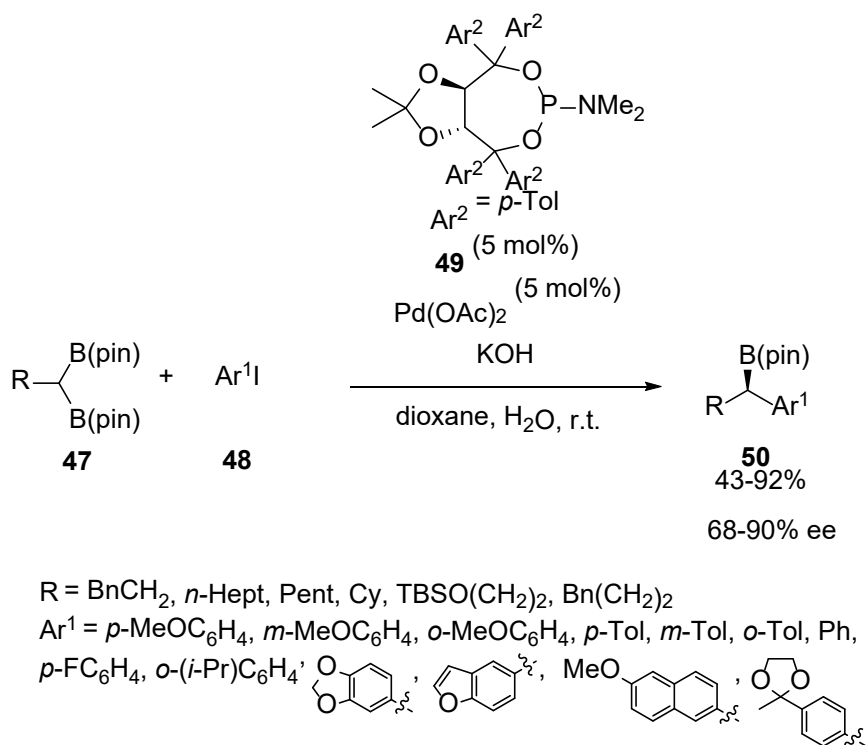
mechanism:



Scheme 22. Coupling of *N*-tosylhydrazones with heterobiaryl bromides [32].

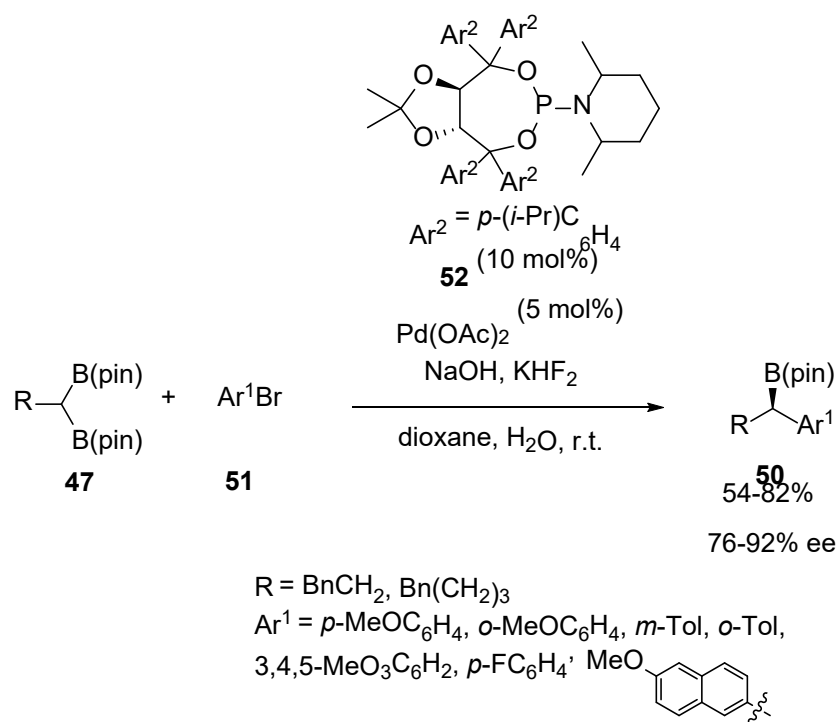
Along with asymmetric $\text{C}(\text{sp}^2)\text{-C}(\text{sp}^2)$ cross-coupling reactions, transition-metal-catalyzed asymmetric cross-couplings with sp^3 carbon represents another useful carbon-carbon bond

forming transformation in organic synthesis to construct carbon stereocenters. An example was described in 2014 by Morken et al., dealing with an enantioselective palladium-catalyzed cross-coupling between achiral geminal bis(boronates) **47** and aryl iodides **48** [33]. It was promoted by a catalyst system composed of 5 mol% of Pd(OAc)₂ and 10 mol% of chiral phosphoramidite **49** in dioxane at room temperature (Scheme 23). It resulted in the formation of the corresponding chiral organoboronates **50** with moderate to high yields (43-92%) and enantioselectivities (68-90% ee). In most cases of differently substituted aryl iodides, the ee values were higher than 80% ee. The lowest enantioselectivity (68% ee) was observed in the reaction of *o*-iodoanisole (Ar¹ = *o*-MeOC₆H₄). The scope of geminal bis(boronates) spanned from linear aliphatic substrates (R = Pent, *n*-Hept) to more hindered substrates (R = Cy). The utility of this novel cross-coupling reaction was demonstrated in a formal asymmetric synthesis of (*R*)-tolterodine which is a drug used in the treatment of urinary incontinence.



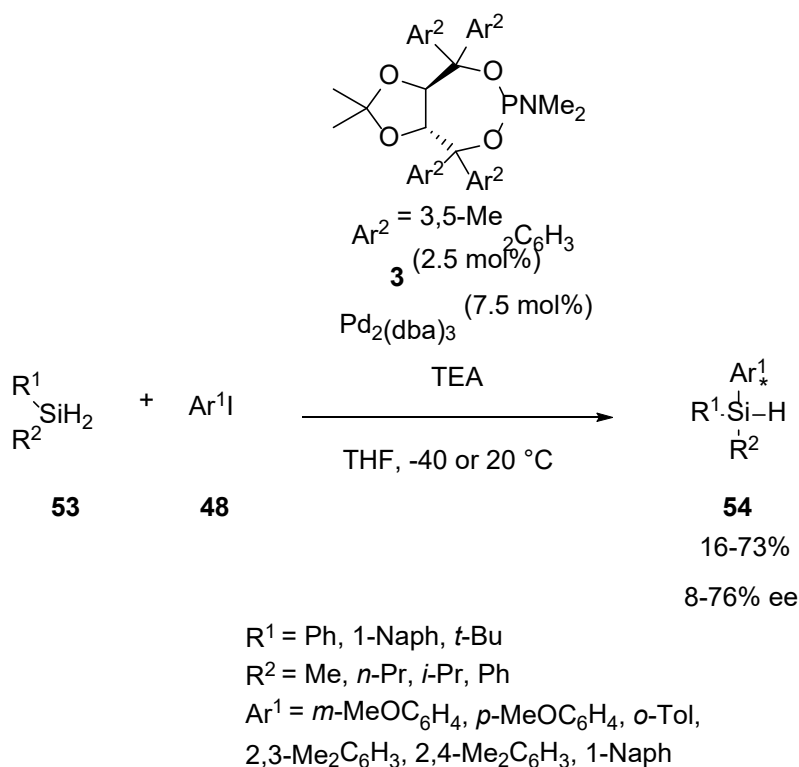
Scheme 23. Coupling of geminal bis(boronates) with aryl iodides [33].

In a related study, Hall et al. reported in 2015 the cross coupling with aryl bromides **51** with geminal bis(boronates) **47** performed in the presence of a closely related chiral phosphoramidite ligand **52** [34]. The desired chiral organoboronates **50** were produced in moderate to good yields (54-82%) and good to high enantioselectivities (76-92% ee), as illustrated in Scheme 24.



Scheme 24. Coupling of geminal bis(boronates) with aryl bromides [34].

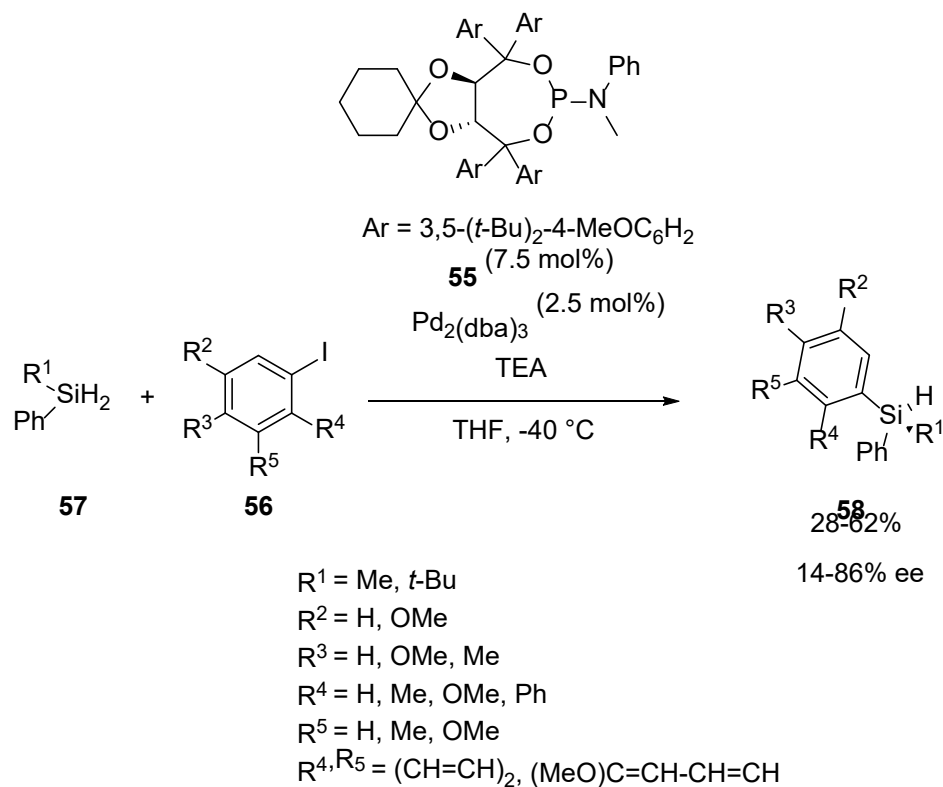
Chiral silanes containing a stereogenic tetrahedral silicon atom are promising chiral reagents, auxiliaries, resolving agents and drug candidates [35]. Although considerable effort has been devoted to their preparation, most popular methodologies are still based on kinetic resolution. Consequently, extensive investigation of silicon–carbon bond-forming transformations has been carried out for the synthesis and application of organosilicon compounds [36]. In this context, Yamanoi and Nishihara introduced in 2012 a novel route to these products involving an efficient enantioselective Si–H functionalization of secondary aryl silanes **53** with aryl iodides **48** [37]. This silicon–carbon bond-forming reaction was promoted by a chiral palladium catalyst in situ generated from 2.5 mol% of Pd₂(dba)₃ and 7.5 mol% of chiral TADDOL-derived phosphoramidite ligand **3** (Scheme 25). Performed at -40 or 20 °C in THF as the solvent, it afforded the corresponding chiral silanes **54** in variable yields (16-73%) and enantioselectivities (8-76% ee). These results indicated that the substitution pattern of the substituent on the phenyl ring of aryl iodides had a major impact on the enantioselectivity of the reaction. Indeed, low ee values were obtained with *meta*- and *para*-substituted aryl iodides (23% ee with Ar = *m*-MeOC₆H₄, 8% ee with Ar = *p*-MeOC₆H₄) while *ortho*-substituted aryl iodides afforded better ee values (51-76% ee).



Scheme 25. Coupling of aryl iodides with dihydrosilanes [37].

Later in 2016, Xu and Yang reinvestigated these reactions by using a bulkier chiral phosphoramidite **55** [38]. The coupling process employed 7.5 mol% of this ligand combined with 2.5 mol% of Pd₂(dba)₃ in THF at -40 °C (Scheme 26). In the presence of TEA as base, the reaction of a series of aryl iodides **56** with dihydrosilanes **57** afforded the corresponding chiral silicon-stereogenic silanes **58** with both low to good yields (28-62%) and enantioselectivities (14-86% ee). The steric repulsion and electronic effect of the substituents exhibited on the phenyl ring of aryl iodides were found to have an impact on the enantioselectivity of the reaction. For example, methoxy-substituted aryl iodides reacted with methylphenylsilane (R¹ = Me) with enantioselectivities decreasing from *ortho*-substituted substrates (R⁴ = OMe: 85% ee) to *para*-substituted ones (R³ = OMe: 14% ee). Furthermore, the reaction of aryl iodide with a 2-methyl substituent (R⁶ = Me) on the aryl ring provided better enantioselectivity (80% ee) than that (21% ee) without a 2-methyl substituent on the aryl ring (R⁶ = H), which indicated the crucial role of the steric effect in the stereoselectivity of the process. In contrast, the crowded 2-iodo-1,3,5-trimethoxybenzene (R³ = R⁴ = R⁶ = OMe) or *tert*-butyl(phenyl)silane (R¹ = *t*-Bu) led to the corresponding silicon-stereogenic silanes in low enantioselectivities (36% and 25% ee, respectively). It must be noted that this

work represented one of the best examples of asymmetric palladium-catalyzed silicon-carbon cross coupling reaction for a stereoselective synthesis of silicon-stereogenic silanes with good enantioselectivity.

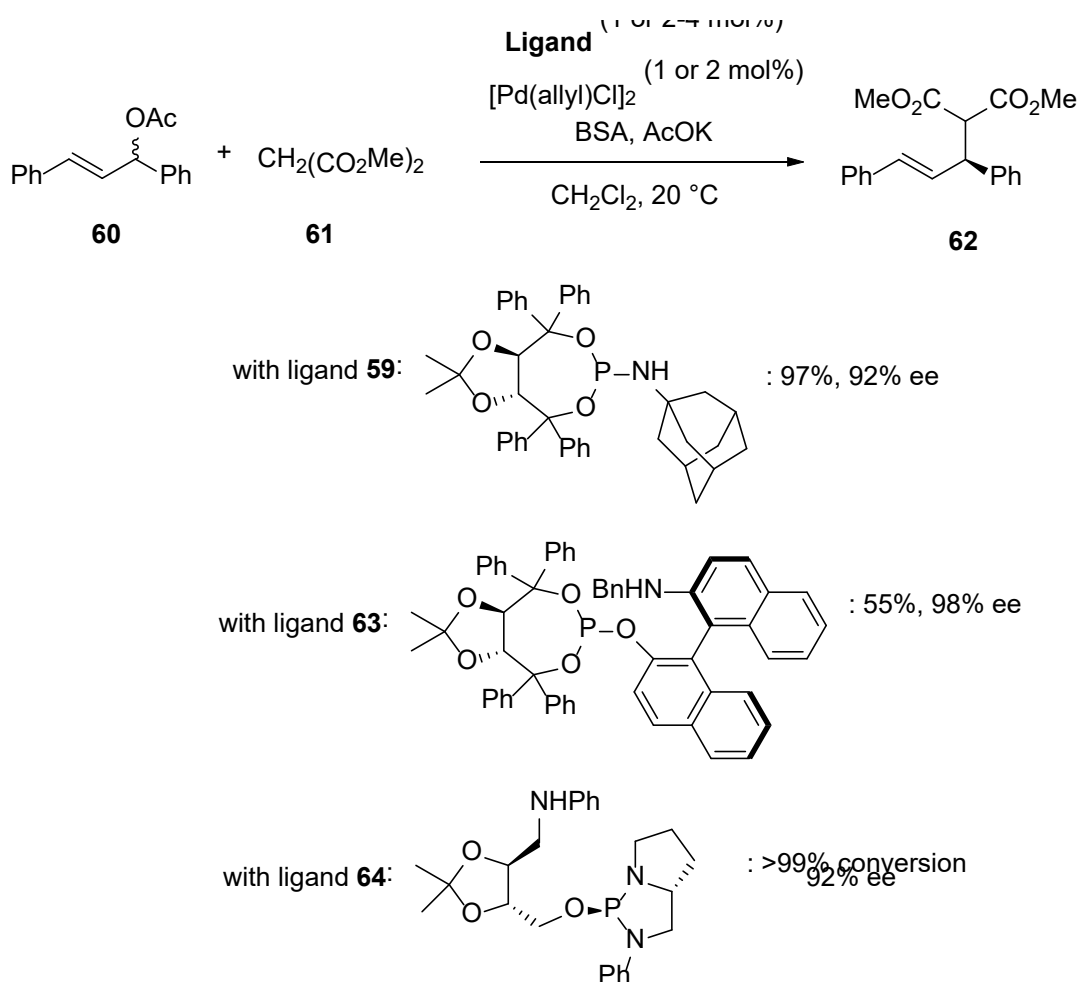


Scheme 26. Coupling of aryl iodides with dihydrosilanes [38].

2.3. Allylic substitutions

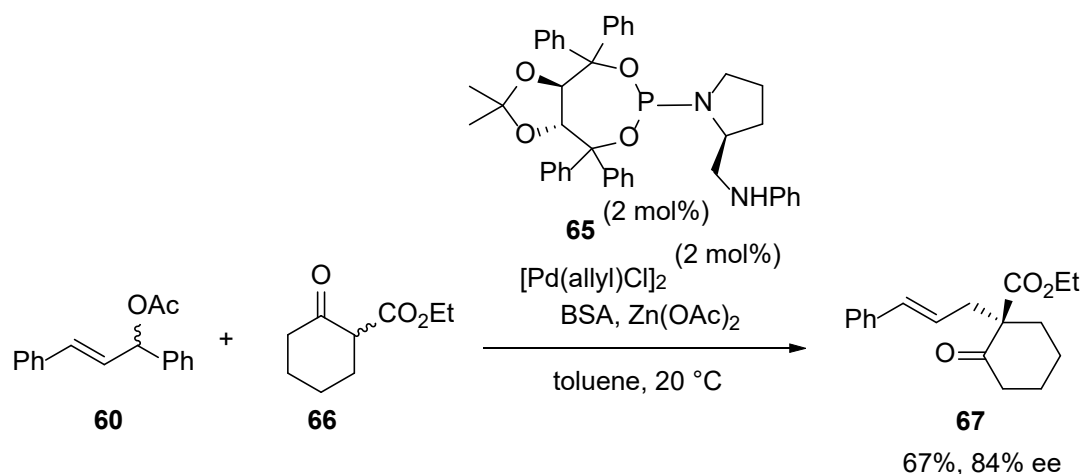
The transition-metal-catalyzed asymmetric allylic substitution has attracted considerable attention owing to its versatile synthetic utilities [39]. The substitution on a π -allylic metal intermediate can lead to various issues including reactivity, regioselectivity, diastereoselectivity and enantioselectivity. Ligand design and substrate selection are the keys to solve these issues. The use of chiral monophosphorous ligands in this area has allowed tremendous progress to be achieved. As an example, Gavrilov et al. employed in 2015 novel chiral TADDOL-derived phosphoramidite ligand **59** to promote the asymmetric palladium-catalyzed asymmetric allylic substitution of (*E*)-1,3-diphenylallyl acetate **60** with dimethyl

malonate **61** [40]. The reaction was performed at 20 °C in dichloromethane as the solvent in the presence of 2 mol% of a combination of ligand **59** with [Pd(allyl)Cl]₂ as precatalyst. It led to the formation of chiral product **62** in 97% yield and 92% ee (Scheme 27). Later in 2017, the same authors reported the synthesis of bulky chiral phosphite P,N-ligand **63** to be investigated in the same reaction [41]. The product was obtained under the same reaction conditions in 55% yield and 98% ee (Scheme 27). Moreover, these authors performed the same reaction in the presence of only 1 mol% of another type of novel chiral phosphorus P,N-ligand **64** under the same conditions, which afforded product **62** with 92% ee and complete conversion (Scheme 27) [42].



Scheme 27. Allylation of dimethyl malonate with (*E*)-1,3-diphenylallyl acetate [40,41,42].

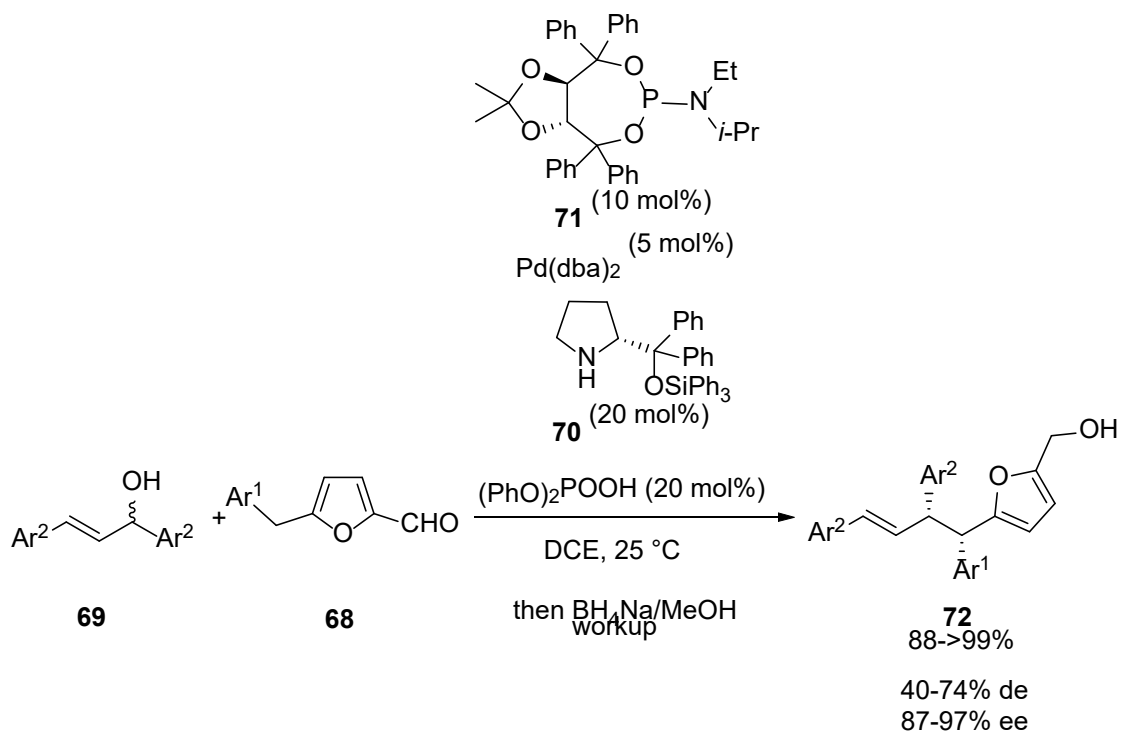
In the same report, the authors also described the synthesis of another novel chiral phosphoramidite P,N-ligand **65** derived from TADDOL to be applied in related reactions [42]. Indeed, the use of 2 mol% of this ligand in combination with the same quantity of [Pd(allyl)Cl]₂ as catalyst system in toluene at 20 °C in the allylic alkylation of (*E*)-1,3-diphenylallyl acetate **60** with ethyl 2-oxocyclohexane-1-carboxylate **66** resulted in the formation of product **67** in 67% yield and 84% ee (Scheme 28).



Scheme 28. Allylation of ethyl 2-oxocyclohexane-1-carboxylate with (*E*)-1,3-diphenylallyl acetate [42].

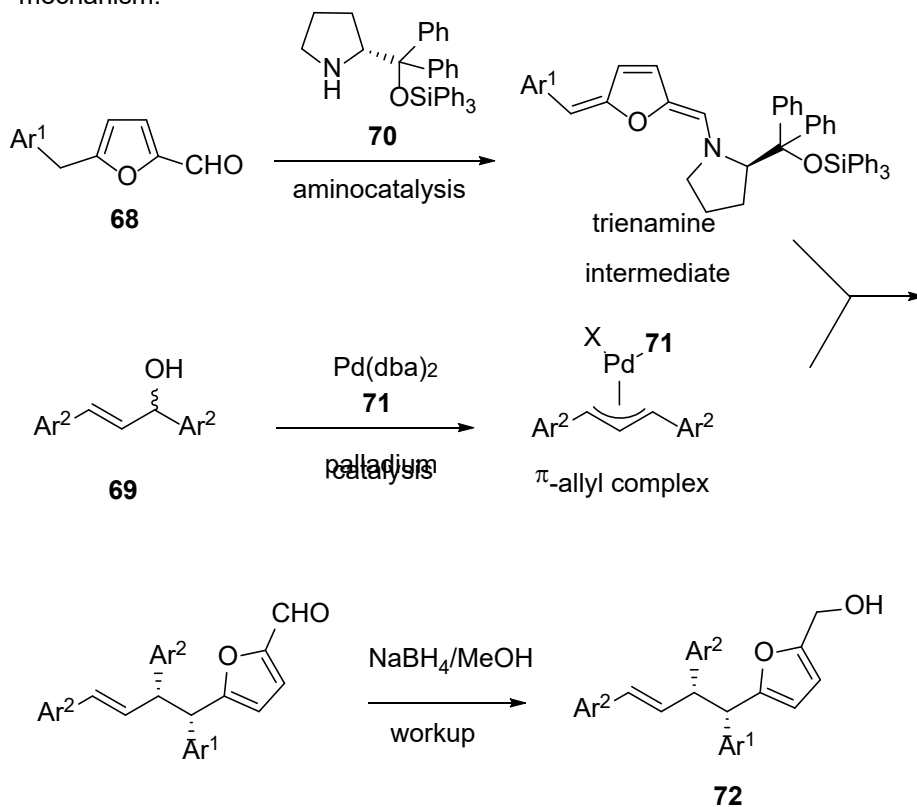
In the last decade, asymmetric multicatalysis has allowed many reactions to be achieved with high stereoselectivities [43]. In most cases, this methodology involves the combination of a chiral organocatalyst [44] with a metal complex. As an example, a palladium/amine cooperative asymmetric catalysis was involved in 2017 by Gong et al. to promote an enantioselective allylic allylation of furfural derivatives **68** with (*E*)-1,3-diarylallyl alcohols **69** [45]. In the presence of 20 mol% of chiral diphenylprolinol silyl ether **70**, 5 mol% of Pd(dba)₂ and 10 mol% of chiral TADDOL-derived phosphoramidite ligand **71**, the asymmetric allylation reaction occurred at the benzylic position of 4-benzyl furfural derivatives **68**, leading to a wide diversity of synthetically useful chiral furanyl methanol derivatives **72** in both high yields (88->99%) and enantioselectivities (87-97% ee) combined with moderate to good diastereoselectivities (40-74% de). As shown in Scheme 29, the synergistic effect of the chiral ligand of palladium catalyst, through the formation of a chiral

π -allyl palladium, combined with that of the chiral organocatalyst through the formation of a trienamine intermediate allowed high levels of stereoselectivities to be achieved. Either electron-donating or electron-withdrawing substituents at the *para*- or *meta*-position of the phenyl ring of the furfural substrate were well tolerated, providing the corresponding products in excellent yields and enantioselectivities along with good diastereoselectivities ($\geq 70\%$ de). However, *ortho*-fluorobenzyl furfural substrate reacted with lower diastereoselectivity (44% de) while combined with 94% ee. Moreover, the catalyst system was compatible to a variety of diaryl-substituted allylic alcohols bearing either electron-donating and electron-withdrawing substituents at the *para*- or *meta*-position of the phenyl ring. This work represented a rare example of combining metal catalysis with trienamine catalysis.



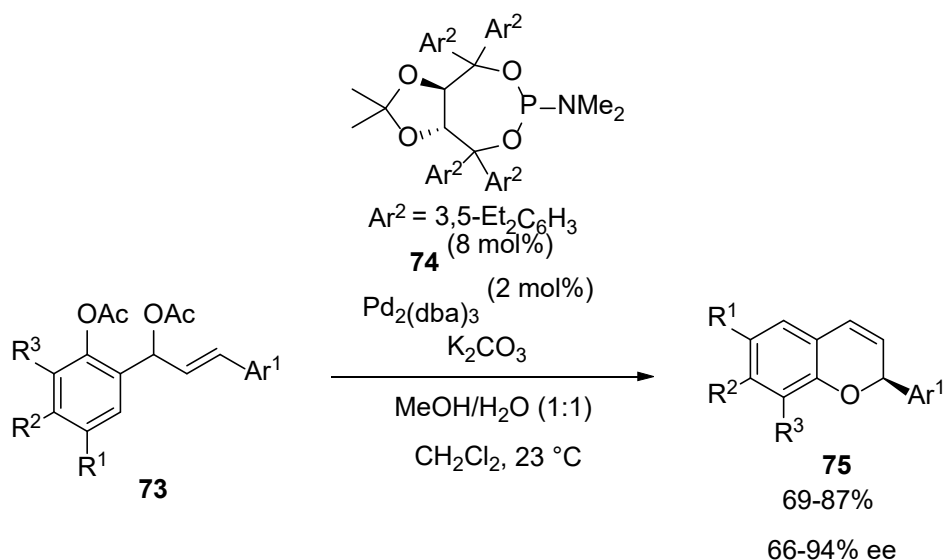
Ar¹ = Ph, *p*-Tol, *p*-MeOC₆H₄, *p*-(*t*-Bu)₂C₆H₃, *p*-FC₆H₄, *p*-ClC₆H₄,
p-F₃CC₆H₄, *m*-Tol, *m*-MeOC₆H₄, *m*-FC₆H₄, 2-Naph, *o*-FC₆H₄
 Ar² = Ph, *p*-Tol, *p*-MeOC₆H₄, *p*-FC₆H₄, *p*-ClC₆H₄, *p*-F₃CC₆H₄,
m-Tol, *m*-MeOC₆H₄, *m*-ClC₆H₄, 2-Naph, 1-Naph

mechanism:



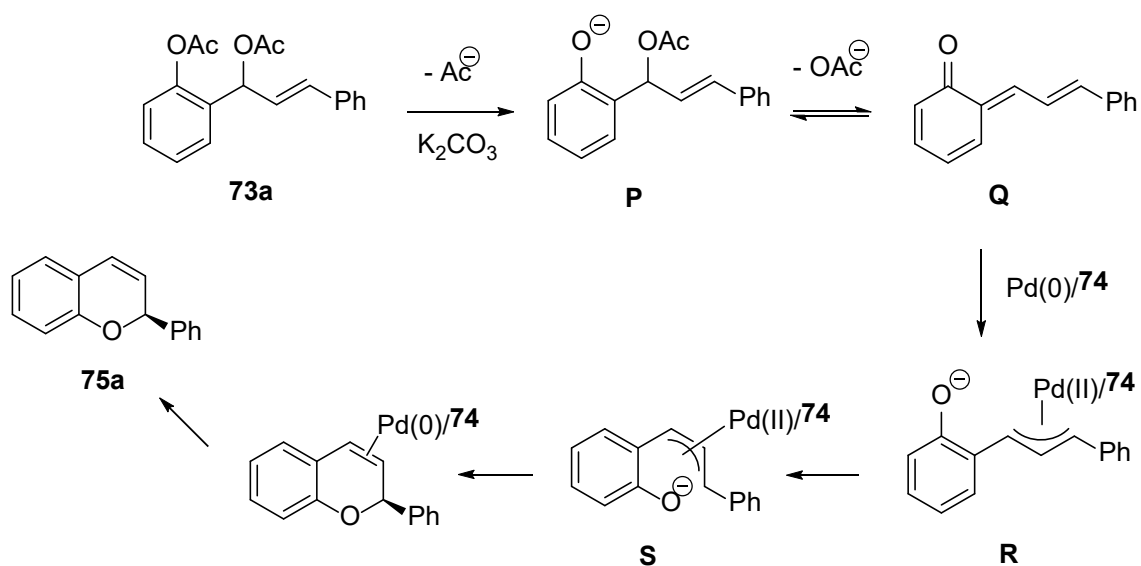
Scheme 29. Allylation of furfural derivatives with (*E*)-1,3-diarylallyl alcohols [45].

Intramolecular allylic aminations and etherifications catalyzed by chiral palladium complexes of TADDOL ligands have also been described. In an example described in 2014, Scheidt et al. reported an enantioselective palladium-catalyzed intramolecular allylic etherification of bis-acetates **73** performed in the presence of 8 mol% of TADDOL-derived chiral phosphoramidite ligand **74** combined with 2 mol% of Pd₂(dba)₃ as precatalyst (Scheme 30) [46]. Carried out at 23 °C in dichloromethane as the solvent and K₂CO₃ as the base, the 6-*endo*-trig allylic substitution resulted in the formation of chiral 2-aryl-2*H*-chromenes **75** in both good to high yields (69-87%) and enantioselectivities (66-94% ee). These products constitute structural motifs present in a myriad of natural products and medicinally important agents. The mechanism depicted in Scheme 30 begins with the deacylation of either enantiomer of the substrate to K₂CO₃ and methanol, producing the nucleophilic phenoxide **P**. This deacylation promotes ejection of the secondary acetate to form achiral *trans*-*o*-quinone methide intermediate **Q**. A subsequent coordination and addition of the chiral palladium complex generates the π-allyl intermediate **R** which undergoes an intramolecular attack of the proximal phenoxide after bond rotation to achieve intermediate **S**. The rate of the *o*-quinone methide formation must be faster than the addition of the chiral palladium catalyst to the substrate or intermediate phenoxide **P**.



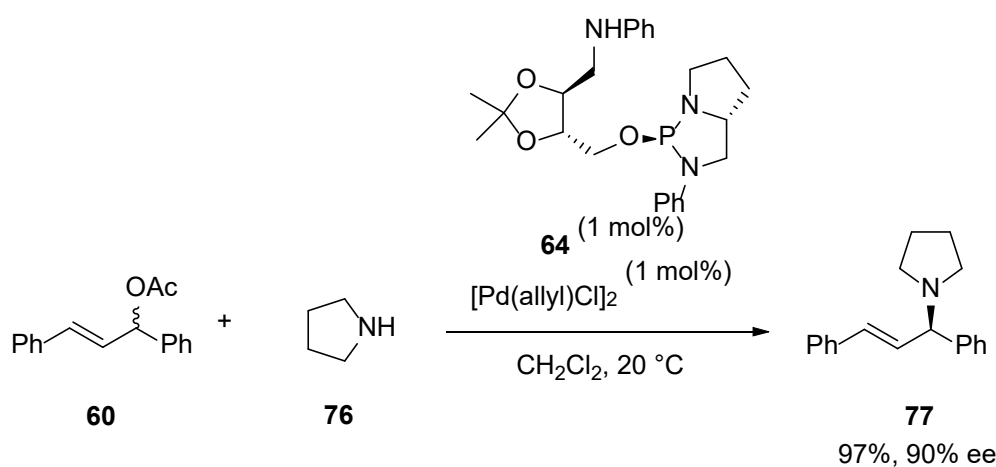
$\text{Ar}^1 = \text{Ph}, 1\text{-Naph}, 2\text{-Naph}, o\text{-Tol}, p\text{-Tol}, m\text{-MeOC}_6\text{H}_4, o\text{-FC}_6\text{H}_4,$
 $p\text{-FC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, 3,4\text{-Cl}_2\text{C}_6\text{H}_3, m\text{-O}_2\text{NC}_6\text{H}_4$
 $\text{R}^1 = \text{H}, \text{F}, \text{OMe}$
 $\text{R}^2 = \text{H}, \text{F}$
 $\text{R}^3 = \text{H}, \text{Me}$

mechanism (with $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}, \text{Ar}_1 = \text{Ph}$):



Scheme 30. Intramolecular allylic etherification of bis-acetates [46].

In addition, moderate enantioselectivities ($\leq 49\%$ ee) were described in 2014 by Schmalz et al. in the palladium-catalyzed *O*-allylation of 4-methoxyphenol using crotyl methyl carbonate by using novel C_2 -symmetric bisphosphine ligands derived from tartaric acid [47]. On the other hand, bulky chiral P,N-ligand **64** was employed in 2017 by Gavrilov et al. at 1 mol% of catalyst loading in combination with the same quantity of $[Pd(allyl)Cl]_2$ in dichloromethane as solvent to promote at 20 °C the asymmetric allylic amination of *E*-1,3-diphenylallyl acetate **60** with pyrrolidine **76** to give the corresponding chiral amine **77** in both excellent yield (97%) and enantioselectivity (90% ee), as shown in Scheme 31 [42].



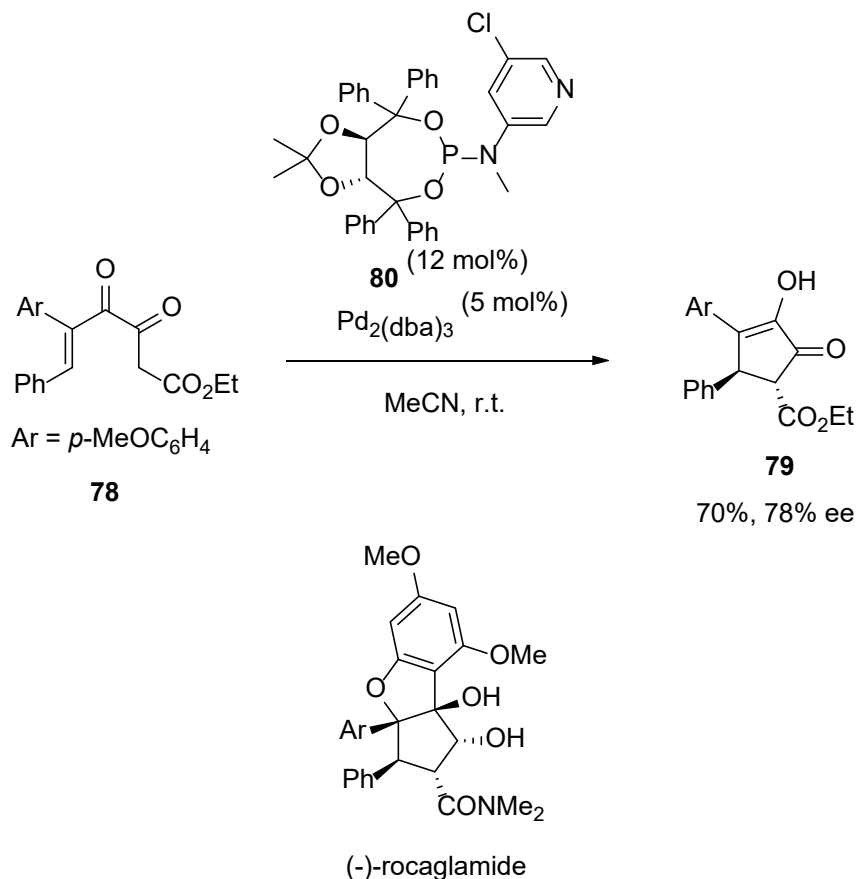
Scheme 31. Allylic amination of *E*-1,3-diphenylallyl acetate with pyrrolidine [42].

2.4. Miscellaneous reactions

2.4.1. Cyclizations

In 2015, Tius and Zhou described the first catalytic asymmetric total synthesis of natural (-)-rocaglamide which exhibits potent cytostatic and anti-inflammatory activities [48]. The key step of this total synthesis was an enantioselective Nazarov-type cyclization of diketoester **78** into the corresponding chiral functionalized cyclopentene **79** achieved with 70% yield and 78% ee (Scheme 32). The cyclization was promoted at room temperature in acetonitrile as the solvent in the presence of 5 mol% of $Pd_2(dba)_3$ combined with 12 mol% of chiral

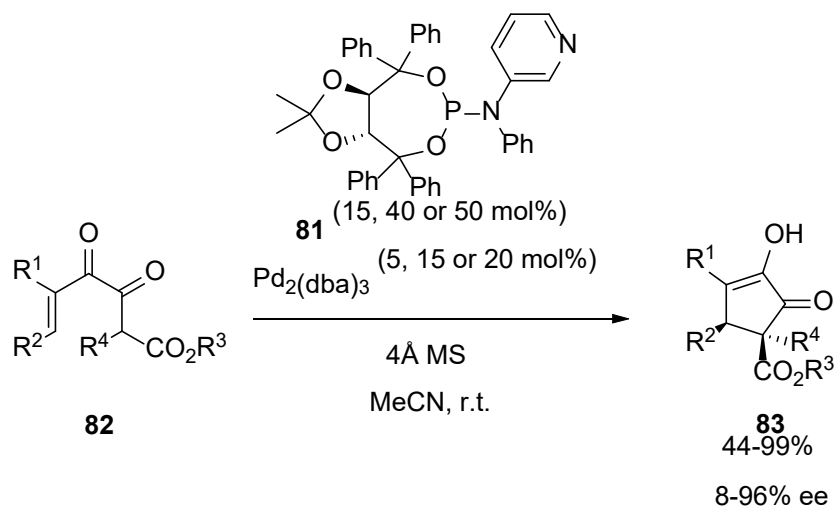
phosphoramidite ligand **80**. The product could be further converted through nine supplementary steps into desired (-)-rocaglamide.



Scheme 32. Nazarov-type cyclization of a diketoester [48].

The scope of the precedent Nazarov-type cyclization reaction could be extended by Tius and Atesin by using a closely related chiral ligand **81** [49]. Indeed, in the presence of 15-50 mol% of this ligand and 5-20 mol% of $\text{Pd}_2(\text{dba})_3$, a wide range of diketoesters **82** were smoothly converted into the corresponding chiral cyclopentenes **83** bearing two contiguous stereocenters, one tertiary and one all-carbon-atom quaternary stereocenter (Scheme 33). The products were produced as single diastereoisomers with moderate to quantitative yields (44-99%) and generally high enantioselectivities (8-96% ee). Actually, ee values were $\geq 82\%$ ee excepted for substrates exhibiting a phenyl or an ethoxy groups at the C5 position ($\text{R}^1 = \text{Ph}$ or OEt) which afforded the corresponding products in much lower enantioselectivities (50% and

8% ee, respectively). The mechanism of the reaction depicted in Scheme 33 evolves through the coordination of the palladium to the alkene group of the substrate followed by enol tautomerization of the diketoester and then concerted proton transfer from the enol to the carbonyl group with the formation of a Pd- π -allyl complex and intramolecular nucleophilic attack to form the desired C-C bond. In the proposed transition state proposed in this Scheme, the P atom and the pyridyl N atom of the ligand occupy two coordination sites on the Pd center.



$R^1 = \text{Me, Et, Ph, OEt}$

$R^2 = \text{Ph, } p\text{-MeOC}$

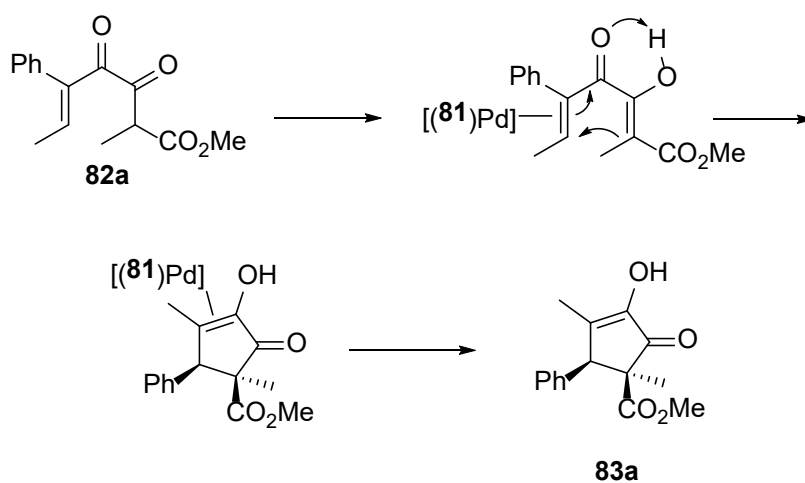
$R^2 = \text{6-H}_4, p\text{-Tol, } p\text{-ClC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, \text{2-furyl, 5-Me-2-furyl, 2-Naph, 1-Naph, Me, Et, } i\text{-Pr, Cy}$

$R^1, R^2 = (\text{CH}_2)_4, (\text{CH}_2)_5$

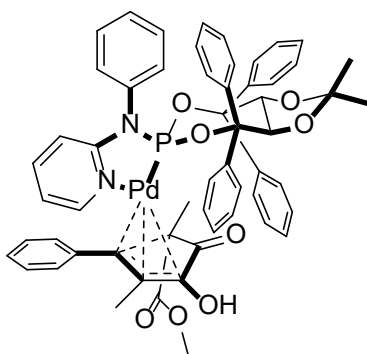
$R^3 = \text{Me, Et}$

$R^4 = \text{Et, } i\text{-Pr, } n\text{-Bu, } n\text{-Dec, Ph}$

mechanism (with $R^1 = R_3 = R_4 = \text{Me}$, $R_2 = \text{Ph}$):

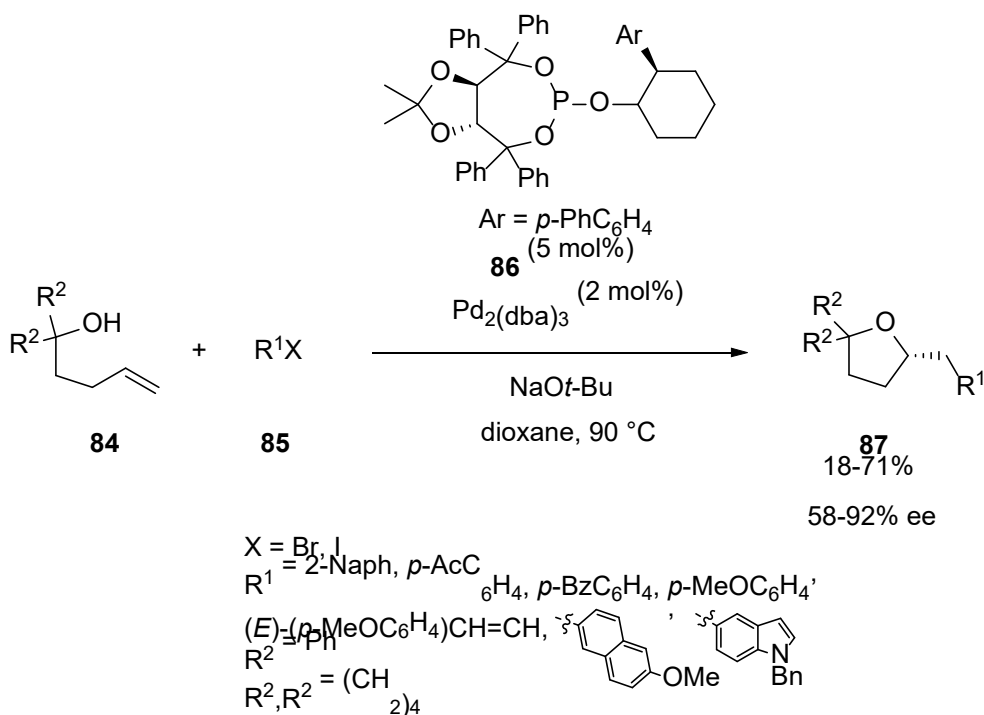


proposed transition state:



Scheme 33. Nazarov-type cyclization of other diketoesters [49].

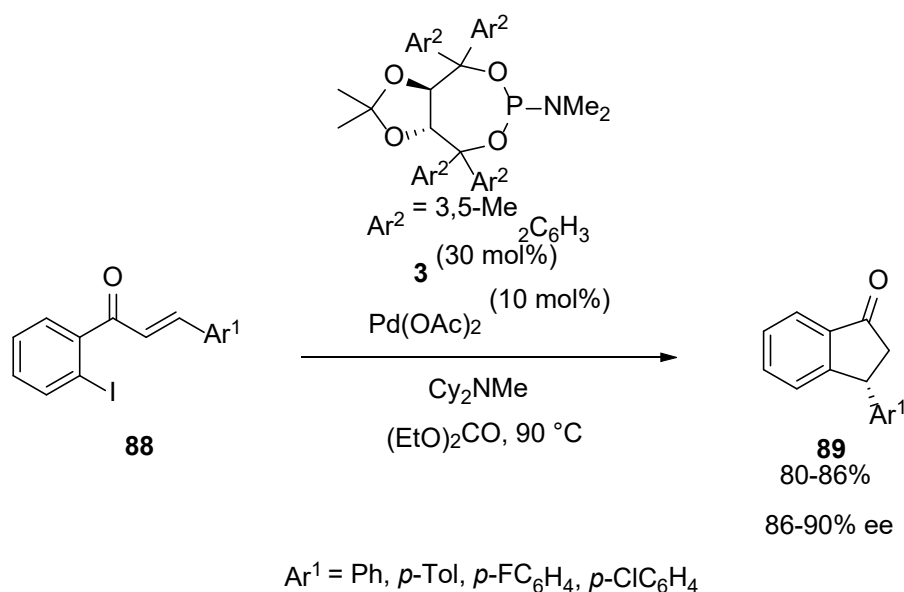
In 2015, Wolfe et al. reported a novel asymmetric synthesis of tetrahydrofurans based on an asymmetric palladium-catalyzed carboalkoxylation reaction of γ -hydroxyalkenes **84** with aryl/alkenyl bromides or iodides **85** [50]. In this context, a fine-tuning of ligands allowed new chiral phosphite **86** to be selected as optimal ligand (Scheme 34). When 5 mol% of the latter was combined with 2 mol% of Pd₂(dba)₃ in dioxane at 90 °C, the carboalkoxylation of a series of γ -hydroxyalkenes **84** with aryl as well as alkenyl halides **85** led to the corresponding chiral substituted tetrahydrofurans **87** in variable yields (18-71%) and moderate to excellent enantioselectivities (58-92% ee).



Scheme 34. Carboalkoxylation reaction of γ -hydroxyalkenes with aryl/alkenyl halides [50].

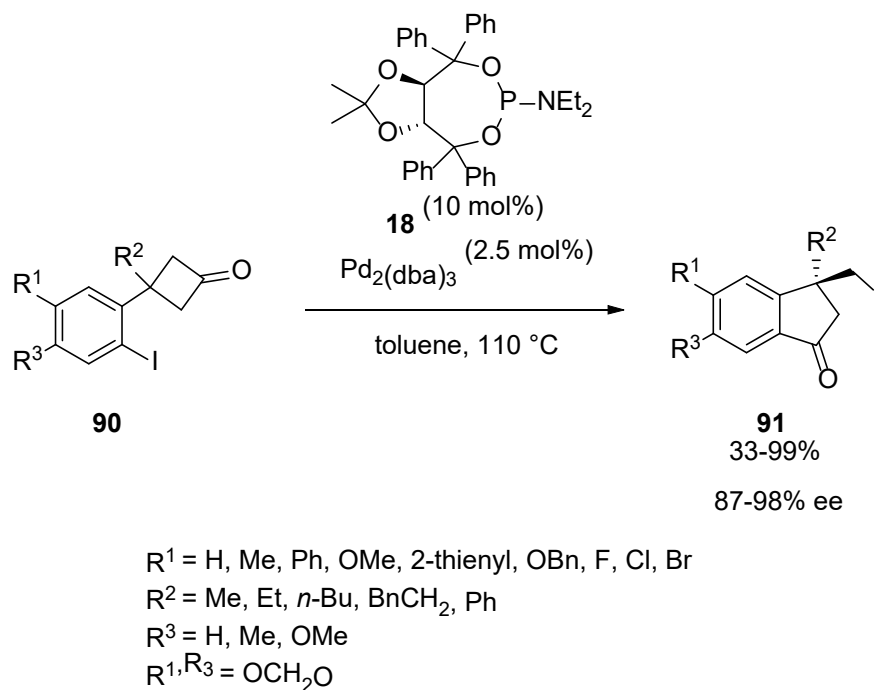
In another area, Minnaard and de Vries reported in 2017 an efficient palladium-catalyzed enantioselective intramolecular reductive Heck reaction of chalcones **88** using 30 mol% of phosphoramidite ligand **3** combined with 10 mol% of Pd(OAc)₂ [51]. The reaction performed

at 90 °C in diethyl carbonate as the solvent led to the corresponding chiral bicyclic products **89** in both high yields (80-86%) and enantioselectivities (86-90% ee), as presented in Scheme 35.



Scheme 35. Intramolecular reductive Heck reaction of chalcones [51].

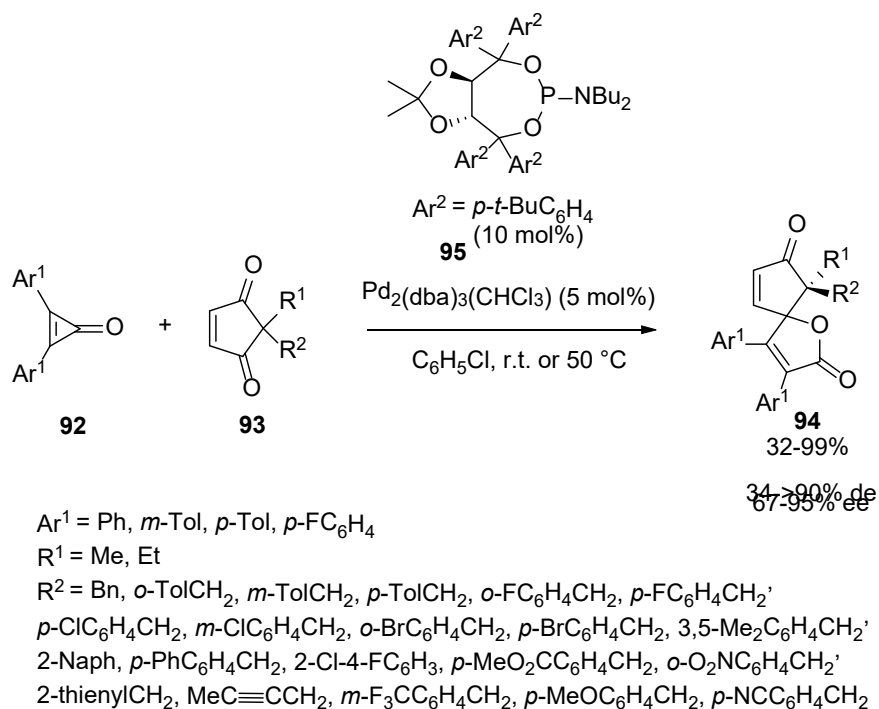
In 2019, Xu, Cao and Xu developed an enantioselective palladium-catalyzed rearrangement of cyclobutanones into chiral indanones (Scheme 36) [52]. The reaction involved a σ -bond cross-exchange through sequential C–C bond activation/alkyl iodide reductive elimination of cyclobutanones **90**. When promoting the reaction by a catalyst derived from 2.5 mol% of $\text{Pd}_2(\text{dba})_3$ and 10 mol% of chiral TADDOL-derived phosphoramidite **18** in toluene at 110 °C, the corresponding chiral indanones **91** bearing an alkyl iodide group and an all-carbon quaternary stereocenter were obtained in moderate to quantitative yields (33-99%) and uniformly excellent enantioselectivities (87-98% ee).



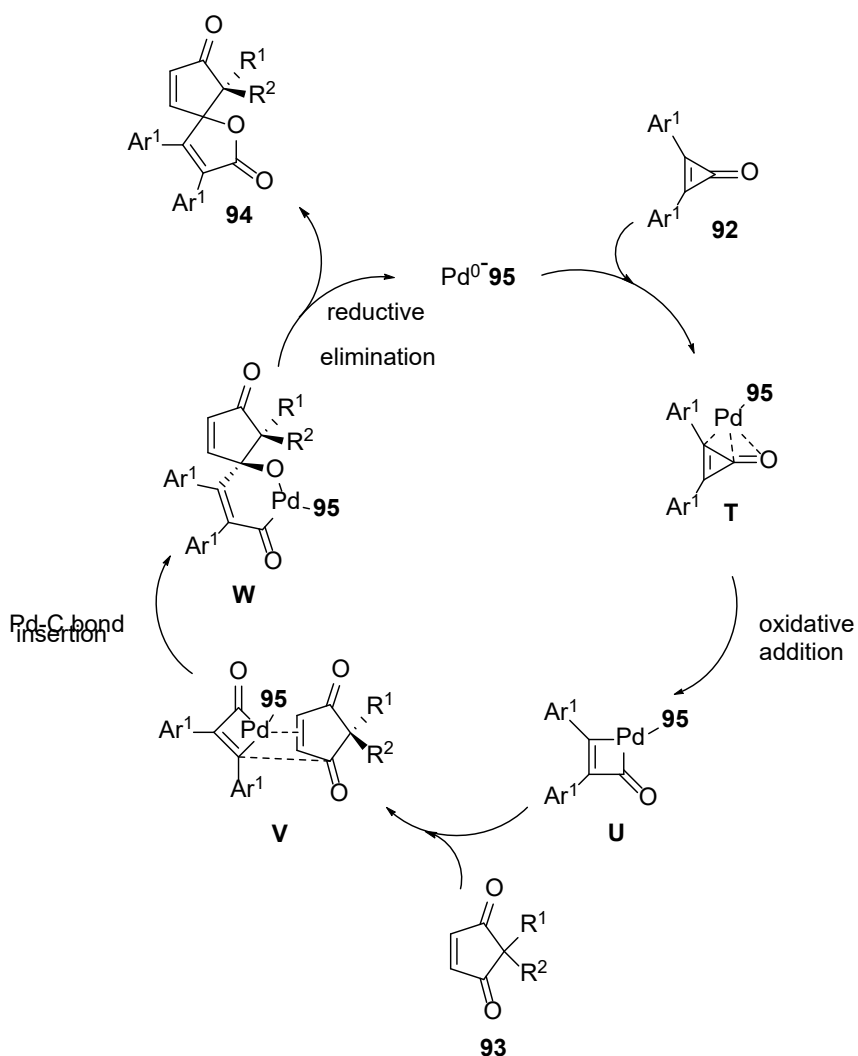
Scheme 36. Rearrangement of cyclobutanones [52].

In 2021, Xu et al. reported an unprecedented enantioselective palladium-catalyzed [3+2] spiroannulation of cyclopropanones **92** with cyclopentene-1,3-diones **93**, allowing a novel and easy access to chiral complex spiranic molecules **94** exhibiting two quaternary adjacent stereocenters [53]. The process, evolving through carbon-carbon bond cleavage followed by [3+2] annulation, was performed at room temperature in chlorobenzene as solvent in the presence of a combination of 5 mol% of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ and 10 mol% of chiral TADDOL-derived phosphoramidite **95**. It delivered a range of oxaspiro cyclopentenone-lactones **94** with moderate to excellent yields (32-99%), diastereo- (>90% de) and enantioselectivities (67-95% ee), as illustrated in Scheme 37. The presence of a wide variety of (functionalized) substituents on the phenyl ring of the benzyl group (R^2) of methyl-substituted cyclopentene-1,3-diones ($\text{R}^1 = \text{Me}$) was well tolerated at *para*-, *ortho*-, or *meta*-position, affording the corresponding products with high yields (80-99%), diastereo- (>90% de) and enantioselectivities (90-93% ee). On the other hand, when the methyl group ($\text{R}^1 = \text{Me}$) on the cyclopentenone was changed into an ethyl group ($\text{R}^1 = \text{Et}$), the reaction required a higher reaction temperature (50 °C vs r.t.) to occur and afforded the corresponding products with lower yields (32-58%), diastereo- (34-50% de) and enantioselectivities (71-85% ee) due to steric hindrance. A possible mechanism is proposed in Scheme 37, beginning with the

coordination of the chiral palladium catalyst to the cyclopropanone to form intermediate **T**. The latter is then submitted to oxidative addition to give intermediate **U** the palladium atom of which subsequently coordinated the carbon-carbon double bond of the cyclopentene-1,3-dione to provide intermediate **V** with the Pd center located on the methyl side because of less steric hindrance. Subsequent migratory insertion of a Pd-C bond into the same-directional ketone group affords intermediate **W**. Finally, the latter undergoes reductive elimination to yield the product along with regenerated catalyst.

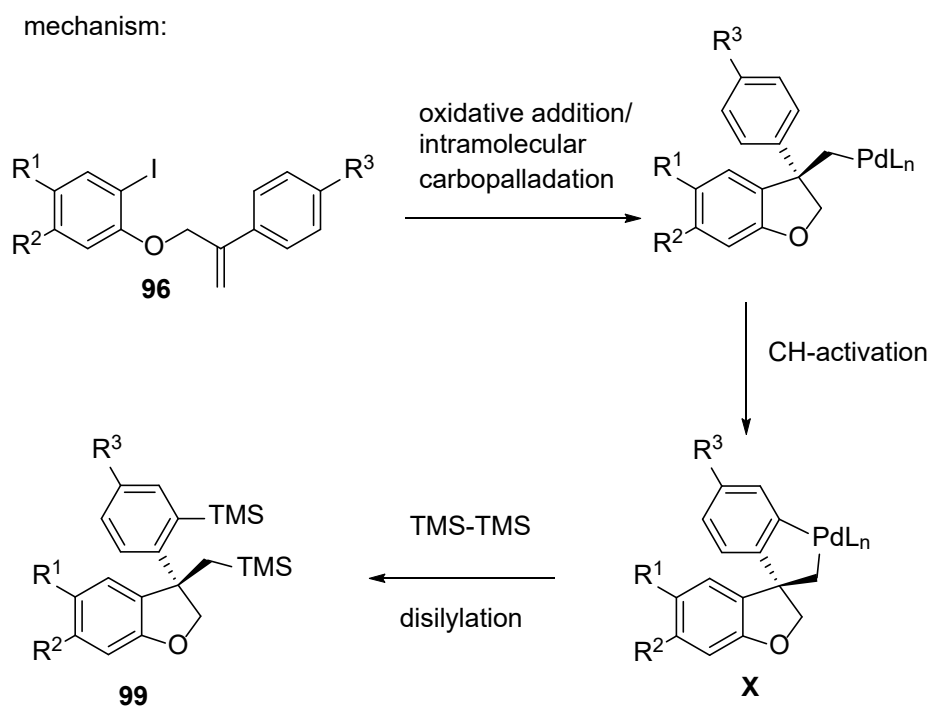
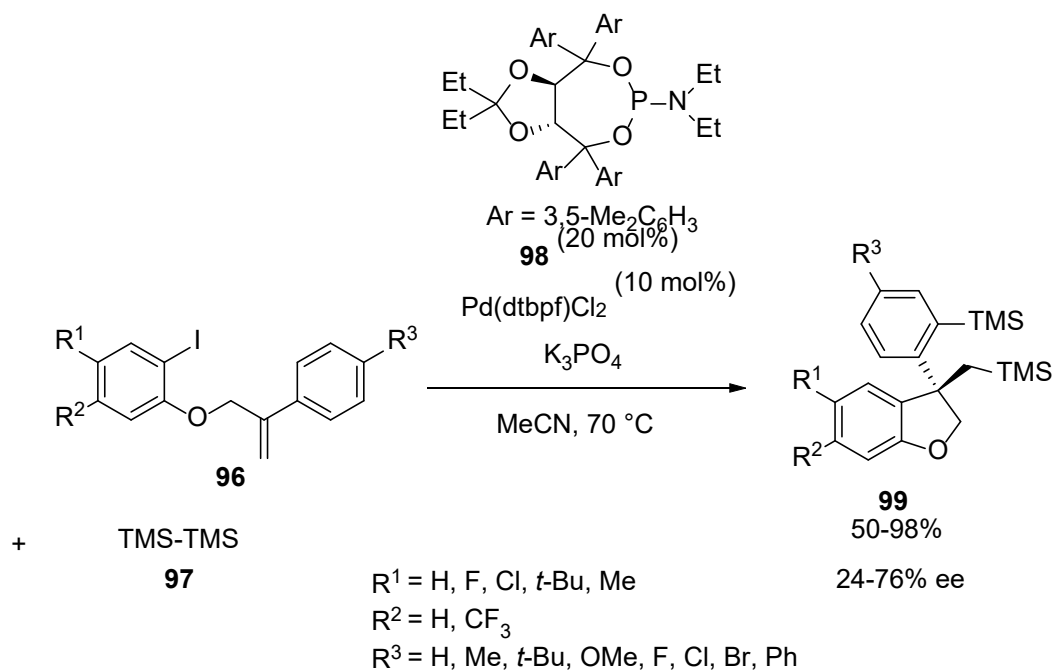


mechanism:



Scheme 37. [3+2] Spiroannulation of cyclopropenones with cyclopentene-1,3-diones [53].

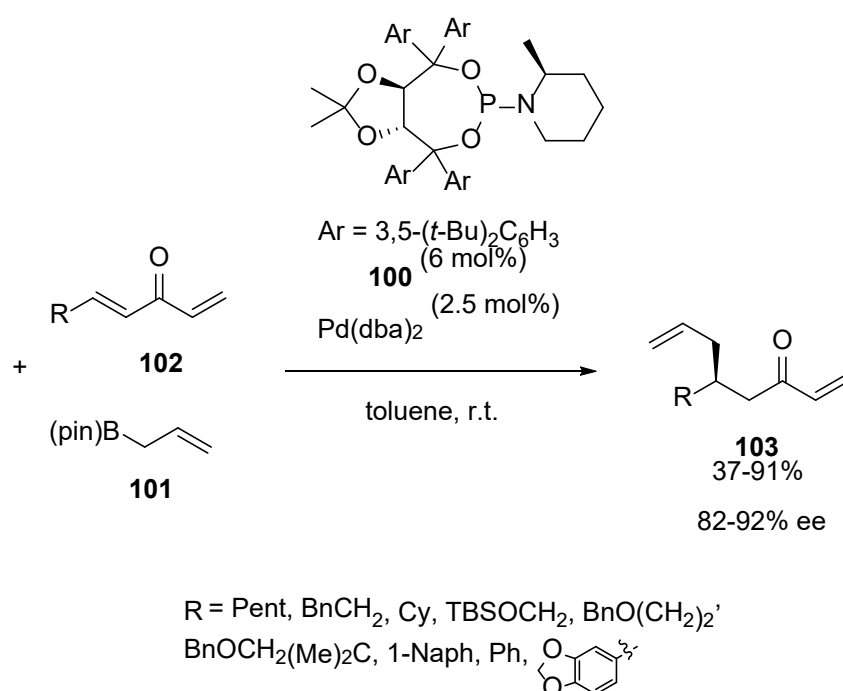
In the same year, these authors also reported an enantioselective palladium-catalyzed domino Heck-type/C–H functionalization/disilylation reaction of aryl iodides **96** with hexamethyldisilane **97** promoted by a chiral palladium catalyst in situ generated from 10 mol% of Pd(dtbpf)Cl₂ and 20 mol% of chiral TADDOL-derived phosphoramidite ligand **98** [54]. In acetonitrile as the solvent, a series of ether-tethered aryl iodides **96** underwent at 70 °C an enantioselective Heck-type/C–H activation to give the corresponding spirocyclic palladacyclopentane intermediate **X** which subsequently reacted with hexamethyldisilane to afford chiral disilylated 2.3-dihydrobenzofuran derivatives **99** (Scheme 38). These disilylated products were obtained with moderate to quantitative yields (50-98%) albeit combined with low to moderate enantioselectivities (24-76% ee). Different substituents (R¹,R²) on the phenyl ring of the aryl iodide were tolerated but in all cases the corresponding products were obtained with variable ee values.



Scheme 38. Domino Heck-type/C–H functionalization/disilylation reaction of aryl iodides with hexamethyldisilane [54].

2.4.2. Acyclic reactions

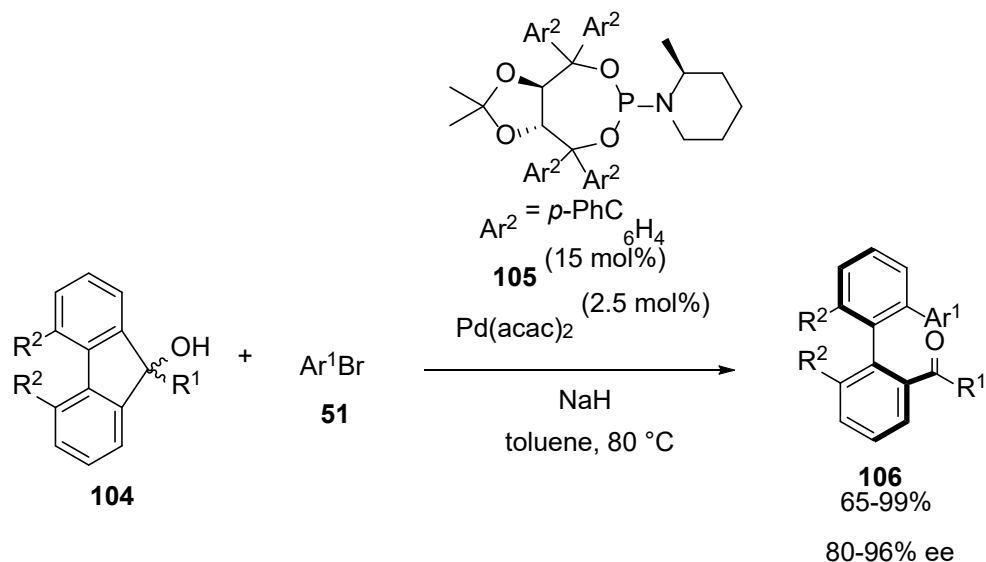
In 2011, Morken et al. selected chiral phosphoramidite ligand **100** to promote the conjugate addition of allylboronic acid pinacol ester **101** to aryl- and alkyl-substituted methyldene ketones **102** (Scheme 39) [55]. The Michael reaction occurred at room temperature in toluene as the solvent in the presence of 6 mol% of ligand **100** and 2.5 mol% of Pd(dba)₂, resulting in the regioselective formation of the corresponding chiral products **103** in moderate to high yields (37-91%) and homogeneously high ee values (82-92% ee).



Scheme 39. Conjugate addition of allylboronic acid pinacol ester to methyldene ketones [55].

In 2019, Gu et al. reported a novel asymmetric synthesis of biaryl atropisomers via palladium-catalyzed chemoselective carbon–carbon cleavage of 9-aryl-9H-fluoren-9-ols **104** with aryl bromides **51** [56]. The process employed a novel chiral phosphoramidite ligand **105** at 15 mol% of catalyst loading combined with 25 mol% of Pd(acac)₂ as precatalyst in toluene as the solvent. It afforded at 80 °C in the presence of NaH as base a remarkably wide diversity of chiral functionalized biaryl products **106** in good to quantitative yields (65-99%) and uniformly high enantioselectivities (80-96% ee), as shown in Scheme 40. It was found that the ring-opening reactivity was considerably accelerated by the torsional strain created by the

steric repulsion between two *ortho*-substituents (R^2) of the biaryl skeleton in the substrates. The catalyst system showed a wide functional group tolerance.



$R^1 = \text{Ph}, p\text{-ClC}_6\text{H}_4, p\text{-Tol}, m\text{-Tol}, 3,5\text{-Me}_2\text{C}_6\text{H}_3, o\text{-Tol}, 2\text{-Naph},$

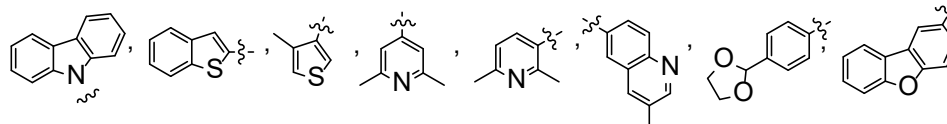
$p\text{-FC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, \text{ferrocenyl}$

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

$Ar^1 = \text{Ph}, o\text{-Tol}, m\text{-Tol}, 3,5\text{-Me}_2\text{C}_6\text{H}_3, p\text{-Tol}, p\text{-F}_3\text{CC}_6\text{H}_4, p\text{-}(t\text{-BuO}_2\text{C})\text{C}_6\text{H}_4,$

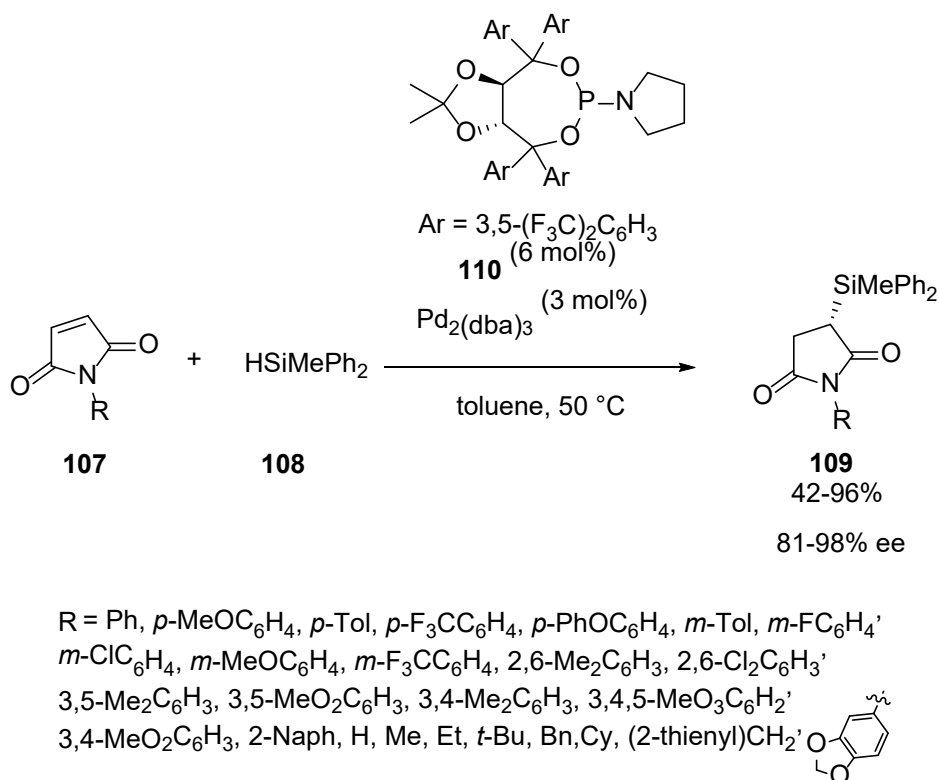
$p\text{-BzC}_6\text{H}_4, p\text{-F}_3\text{COC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, p\text{-}(\text{Ph}_2(\text{O})\text{P})\text{C}_6\text{H}_4, 3,5\text{-Ph}_2\text{C}_6\text{H}_3, 2\text{-Naph},$

$o\text{-MeOC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-}(\text{CH}_2=\text{CH})\text{C}_6\text{H}_4, p\text{-}(\text{TMSC}\equiv\text{C})\text{C}_6\text{H}_4, 2\text{-thienyl},$



Scheme 40. Ring-opening of 9-aryl-9H-fluoren-9-ols with aryl bromides [56].

In 2020, Xu et al. reported a highly enantioselective hydrosilylation of carbonyl-activated alkenes, such as *N*-aryl- and *N*-alkylmaleimides **107**, with methyl diphenylsilane **108** into the corresponding chiral silyl succinimides **109** promoted by 6 mol% of chiral phosphoramidite ligand **110** and 3 mol% of $\text{Pd}_2(\text{dba})_3$ [57]. As shown in Scheme 41, the products were formed in moderate to excellent yields (42-96%) and uniformly high enantioselectivities (81-98% ee).



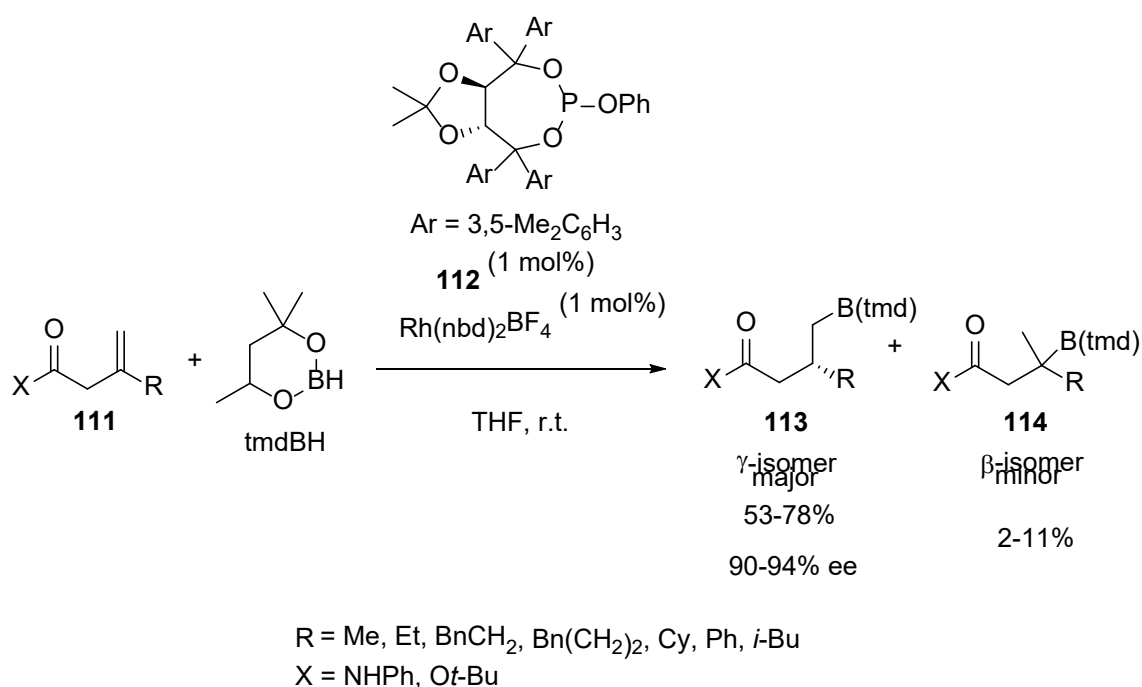
Scheme 41. Hydrosilylation of maleimides [57].

3. Enantioselective rhodium-catalyzed reactions

3.1. Hydroborations

Chiral organoboronates are useful synthetic intermediates for a number of stereospecific transformations [58]. In this context, their asymmetric preparation are challenging. TADDOL-derived phosphorus ligands have proven to be highly effective in a variety of transition-metal-catalyzed hydroboration reactions. In an example reported in 2012, Takacs et al. described an enantioselective hydroboration of challenging 1,1-disubstituted alkenes **111** with 4,4,6-tri-methyl-1,3,2-dioxaborinane (tmdBH) [59]. The reaction was promoted at room temperature in THF as the solvent by 1 mol% of a chiral rhodium catalyst derived from Rh(nbd)₂BF₄ and chiral TADDOL-based phosphite ligand **112** (Scheme 42). It afforded regioselectively the corresponding chiral γ -borylated products **113** as major products in

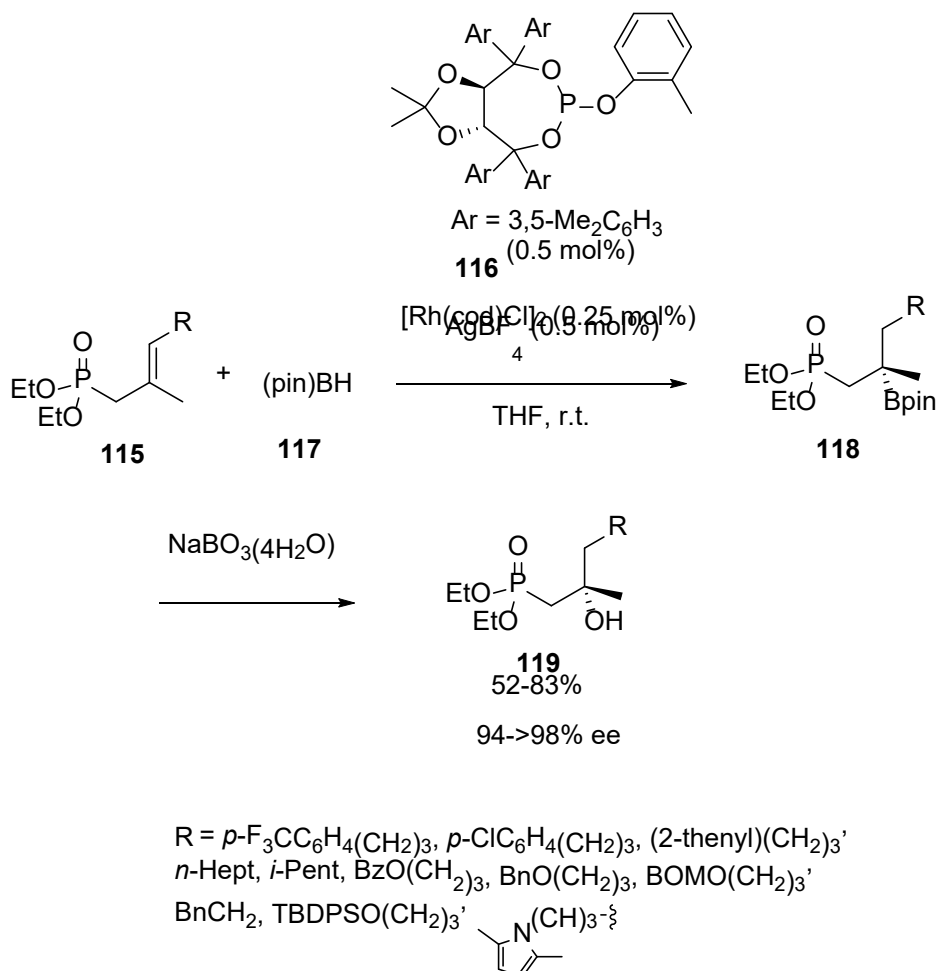
moderate to good yields (53-78%) along with minor β -borylated products **114** (2-11% yield). The major regioisomers **113** were obtained in uniformly excellent enantioselectivities (90-94% ee). The catalyst system tolerated both phenyl-substituted amides (X = NHPH) and β,γ -unsaturated *tert*-butyl esters (X = *Ot*-Bu).



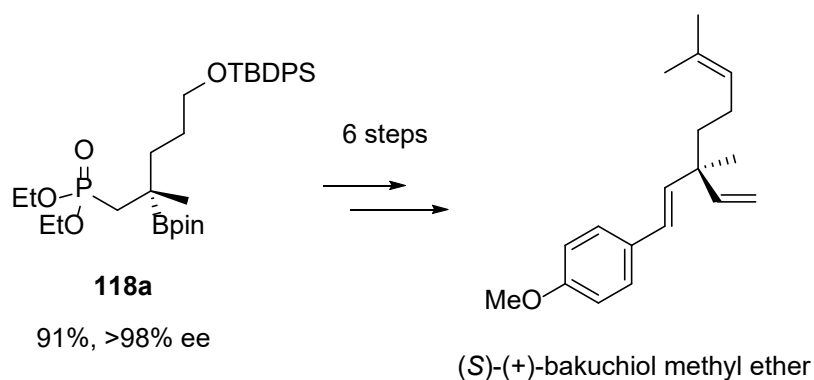
Scheme 42. Hydroboration of 1,1-disubstituted alkenes with tmdBH [59].

While commercial $\text{Rh}(\text{nbd})_2\text{BF}_4$ is a suitable catalyst precursor, a catalyst generated in situ from $[\text{Rh}(\text{cod})\text{Cl}]_2$ and AgBF_4 , in combination with a TADDOL-derived chiral phosphite ligand is more economic. In 2017, Takacs and Chakrabarty employed such a catalyst system to promote the highly enantioselective rhodium-catalyzed phosphonate-directed hydroboration of allylic phosphonates **115** with pinacolborane **117** [60]. As presented in Scheme 43, the reaction was performed at room temperature in THF as the solvent in the presence of a combination of 0.25 mol% of $[\text{Rh}(\text{cod})\text{Cl}]_2$, 0.5 mol% of AgBF_4 and 0.5 mol% of TADDOL-based phosphite ligand **116**. In this case of substrates, the reaction resulted in the regioselective formation of chiral β -borylated phosphonates **118** which were subsequently converted into the corresponding chiral β -hydroxyphosphonates **119** bearing a quaternary carbon stereocenter with good to high yields (52-83%) and remarkable enantioselectivities

(94->98% ee). The utility of the methodology was illustrated by a synthesis of natural product (S)-(+)-bakuchiol methyl ether.

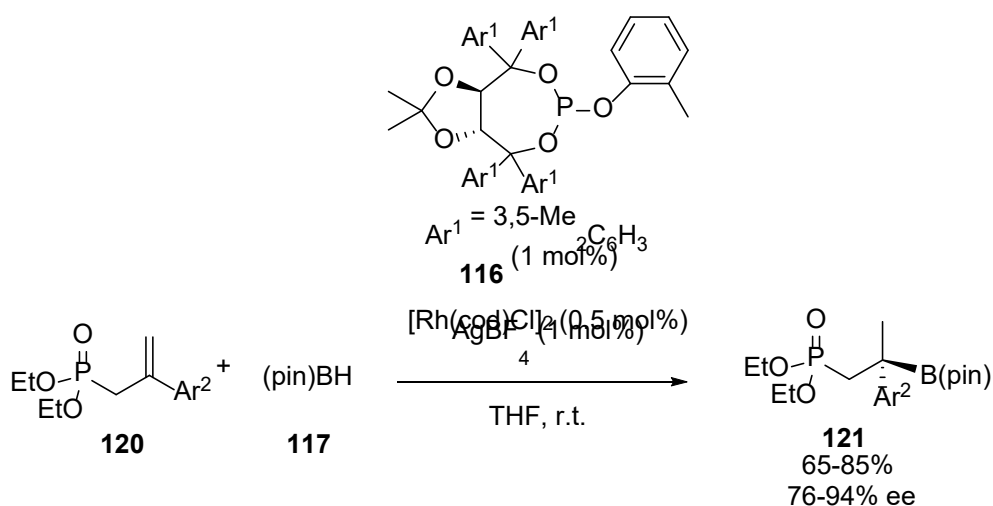


synthesis of (S)-(+)-bakuchiol methyl ether:



Scheme 43. Hydroboration of allylic phosphonates with (pin)BH [60].

Later in 2021, the same group extended the scope of this methodology to other allylic phosphonates, such as β -(hetero)aryl-substituted methylenes **120** bearing a phosphonate moiety [61]. In this case, 0.5 mol% of the same rhodium precatalyst was used along with 1 mol% of AgBF_4 and 1 mol% of the same phosphite ligand **116**. The asymmetric hydroboration with pinacolborane delivered boron predominantly to the more substituted β -position, resulting in the regioselective formation of chiral tertiary benzylic boronic esters **121** in both good to high yields (65-85%) and enantioselectivities (76-94% ee), as illustrated in Scheme 44. Furthermore, the catalyst system could also be applied to the more challenging asymmetric hydroboration of β -aryl-trisubstituted alkenes **122**, which afforded regio- and diastereoselectively the corresponding chiral tertiary benzylic boronic esters **123** in both moderate to high yields (56-84%) and ee values (66-94% ee), as shown in Scheme 44.



$\text{Ar}^2 = m\text{-MeOC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, 3,5\text{-Me}_2\text{C}_6\text{H}_3, p\text{-Tol}, p\text{-F}_3\text{CC}_6\text{H}_4,$
 $p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, 2\text{-thienyl}, 1\text{-thienyl},$

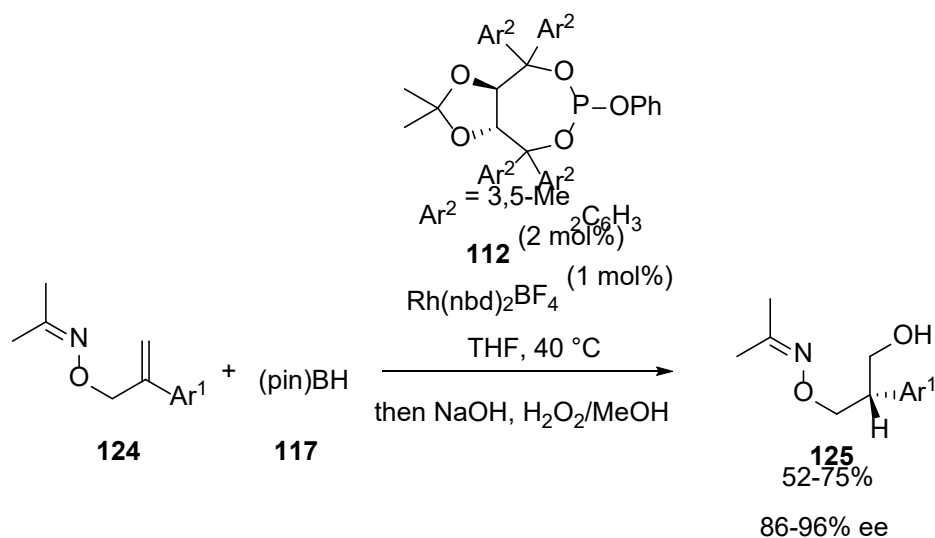


$\text{Ar}^2 = \text{Ph}, 1\text{-thienyl}, p\text{-MeOC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4,$
 $p\text{-F}_3\text{CC}_6\text{H}_4,$

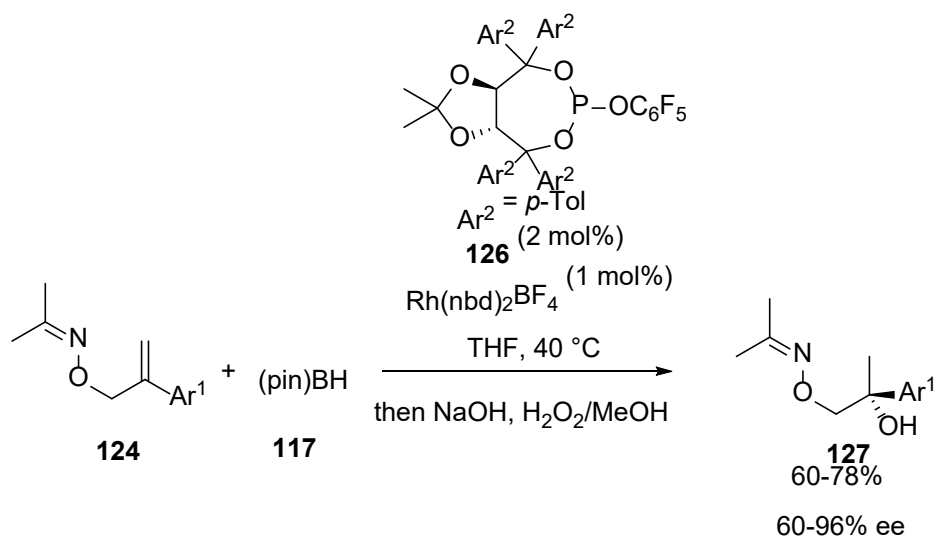
Scheme 44. Hydroborations of β -(hetero)aryl-substituted methylidenes and β -aryl-trisubstituted alkenes [61].

In 2019, the same authors demonstrated that relatively modest changes into the structure of the chiral TADDOL-derived phosphite ligands employed resulted in a switch in both the regioselectivity and the sense of the enantioselectivity in the catalytic asymmetric hydroboration of β -aryl methylidenes **124** with pinacolborane **117** [62]. As depicted in Scheme 45, an asymmetric rhodium-catalyzed γ -boration at the unsubstituted terminus of

alkenes **124** led to the corresponding chiral primary organoboronic esters **125** when performed in the presence of 2 mol% of chiral phosphite ligand **112** combined with 1 mol% of Rh(nbd)₂BF₄. On the other hand, in the presence of closely related chiral phosphite ligand **126**, an asymmetric β-boration of alkenes **124** with pinacolborane occurred under similar conditions, resulting in the formation of the corresponding chiral tertiary organoboronic esters **127**. Products **125** were obtained in good yields (52-75%) and uniformly high enantioselectivities (86-96% ee) while products **127** were produced in slightly better yields (60-78%) and moderate to high ee values (60-96% ee). In all cases, the regioselectivity values reached greater than 95:5. These results showed that small differences in the TADDOL-derived chiral monophosphite ligands used in the hydroboration with pinacolborane selectively produced either chiral primary or tertiary borated products. Indeed, the nature of the TADDOL backbone substituents and that of the phosphite moiety function could synergistically direct the sense and extent of regioselectivity and enantioinduction.



$\text{Ar}^1 = p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-MeO}_2\text{CC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, p\text{-Tol}, p\text{-MeOC}_6\text{H}_4, p\text{-Me}_2\text{NC}_6\text{H}_4, p\text{-(BocNH)C}_6\text{H}_4$



$\text{Ar}^1 = p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-MeO}_2\text{CC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, p\text{-Tol}, p\text{-MeOC}_6\text{H}_4, p\text{-Me}_2\text{NC}_6\text{H}_4, p\text{-(BocNH)C}_6\text{H}_4$

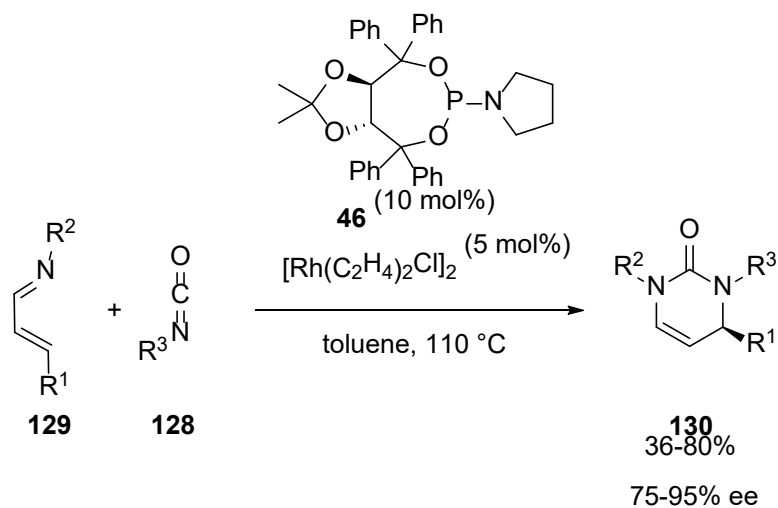
Scheme 45. Hydroborations of β -aryl-substituted methylidenes [62].

In addition, the same authors earlier described in 2012 the synthesis of heterobimetallic supramolecular catalysts bearing TADDOL-derived phosphites which were further investigated as promoters in the asymmetric rhodium-catalyzed hydroboration of *meta*-substituted styrenes varying in steric and electronic character [63]. Systematic changes in the

structures of the scaffold and ligating groups permitted fine tuning of the supramolecular catalyst to achieve high α -regioselectivity (95-98%) and high enantioselectivity (94-97% ee).

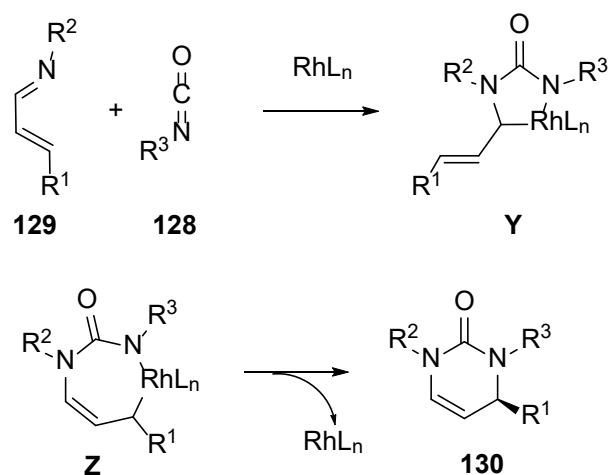
3.2. Cycloadditions/cyclizations

In 2011, Rovis and Oberg reported an asymmetric rhodium-catalyzed [4+2] cycloaddition of α,β -unsaturated imines **129** with isocyanates **128** (Scheme 46) [64]. By using 10 mol% of chiral phosphoramidite **46** as the ligand and 5 mol% of $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ as the precatalyst, a series of chiral pyrimidinones **130** were synthesized in moderate to high yields (36-80%) and good to excellent enantioselectivities (75-95% ee). The authors proposed the mechanism depicted in Scheme 43 involving an initial coordination of the α,β -unsaturated imine and isocyanate by the rhodium catalyst followed by an oxidative cyclization to generate rhodacycle **Y**. Then, the latter underwent a η^1 - η^3 - η^1 shift to form seven-membered rhodacycle **Z** that led through a reductive elimination to the final pyrimidinone along with the regenerated catalyst.



$\text{R}^1 = \text{Ph}, o\text{-MeOC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, p\text{-O}_2\text{NC}_6\text{H}_4,$
 2-furyl, (*E*)-MeCH=CH, *n*-Pr, *i*-Pr
 $\text{R}^2 = \text{Ph}, p\text{-MeOC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, \text{Cy}, \text{BnCH}_2, \text{PMB}, \text{Bn}$
 $\text{R}^3 = \text{Hex}, \text{PMB}, \text{Ph}, \text{CH}_2=\text{CH}(\text{CH}_2)_3$

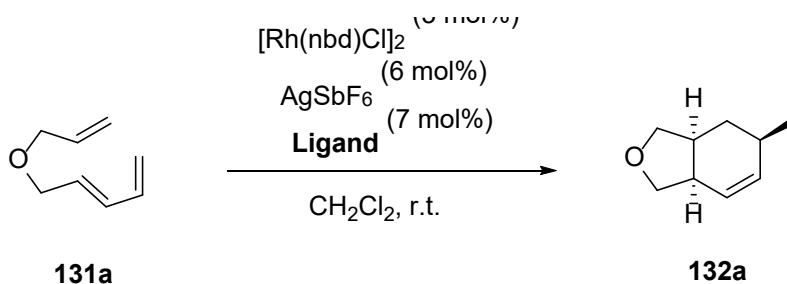
possible mechanism:



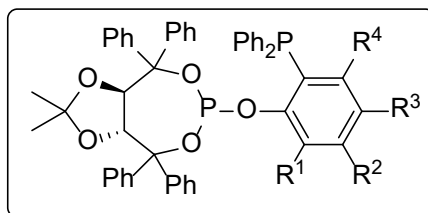
Scheme 46. [4+2] Cycloaddition of α,β -unsaturated imines with isocyanates [64].

The same year, Schmalz et al. developed asymmetric intramolecular [4+2] cycloaddition of trienes **131** into the corresponding chiral bicyclic products **132** promoted by novel chiral rhodium catalysts generated by microwave-assisted catalyst conditioning from $[\text{Rh}(\text{nbd})\text{Cl}]_2$, a phosphite ligand and AgSbF_6 (Scheme 47) [65]. In a first time, different types of chiral phenol-derived phosphite ligands **133** and **L1-L9** were investigated in the [4+2] cycloaddition of triene **131a** ($\text{X} = \text{O}$) into the corresponding chiral bicyclic product **132a** in dichloromethane

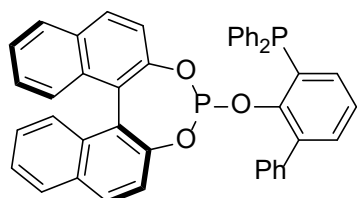
as solvent. The reaction was performed at room temperature in the presence of 3 mol% of $[\text{Rh}(\text{nbd})\text{Cl}]_2$, 6 mol% of AgSbF_6 and 7 mol% of chiral ligand. Despite their seemingly structural similarity, the ligands were found to behave quite differently. Most importantly, a tremendous effect of the phenolic backbone substitution pattern on both the activity and enantioselectivity of the catalyst was observed. While a methyl substituent in the R^4 position of the ligand strongly reduced the activity, the variation of the substituent R^1 (*ortho* to the phosphite moiety) had a great impact on the enantioselectivity. Ligands **L1**, **133** and **L9** led to full conversion while a promising enantioselectivity (62% ee) was found only for the phenyl-substituted ligands **133** and **L9**. Exchanging the TADDOL unit for BINOL (**133**→**L8**) led to a dramatic decrease in enantioselectivity (62% ee for **132a** with ligand **133** vs 25% ee for *ent*-**132a** with ligand **L8**). The fluorophenyl-TADDOL-based ligand **L9** provided the same results (62% ee) than its non-fluorinated congener **133**. On the basis of these results, the authors selected optimal ligand **133** to optimize the reaction conditions.



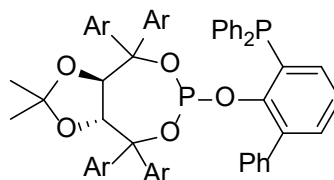
with ligands:



- L1:** $R^1 = R^2 = Me, R^3 = R^4 = H$: *ent*-**132a**, 6% ee
L2: $R^1 = i-Bu, R^2 = R^3 = R^4 = H$: *ent*-**132a**, 6% ee
L3: $R^1 = i-Pr, R^2 = R^3 = R^4 = H$: *ent*-**132a**, 5% ee
L4: $R^1 = i-Pr, R^2 = R^3 = H, R^4 = Me$: no reaction
L5: $R^1 = R^4 = Me, R^2 = R^3 = H$: **132a**, 48% ee
L6: $R^1 = R^3 = i-Bu, R^2 = R^4 = H$: *ent*-**132a**, 7% ee
L7: $R^1 = Me, R^2 = R^3 = R^4 = H$: *ent*-**132a**, 8% ee
133: $R^1 = Ph, R^2 = R^3 = R^4 = H$: **132a**, 62% ee



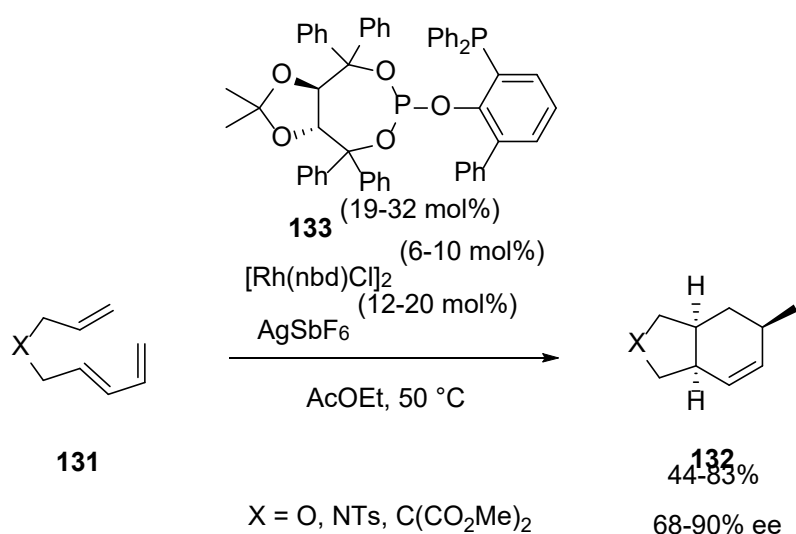
L8: Ar = *p*-F-C₆H₄: *ent*-**132a**, 25% ee



L9: Ar = *p*-F-C₆H₄: **132a**, 62% ee

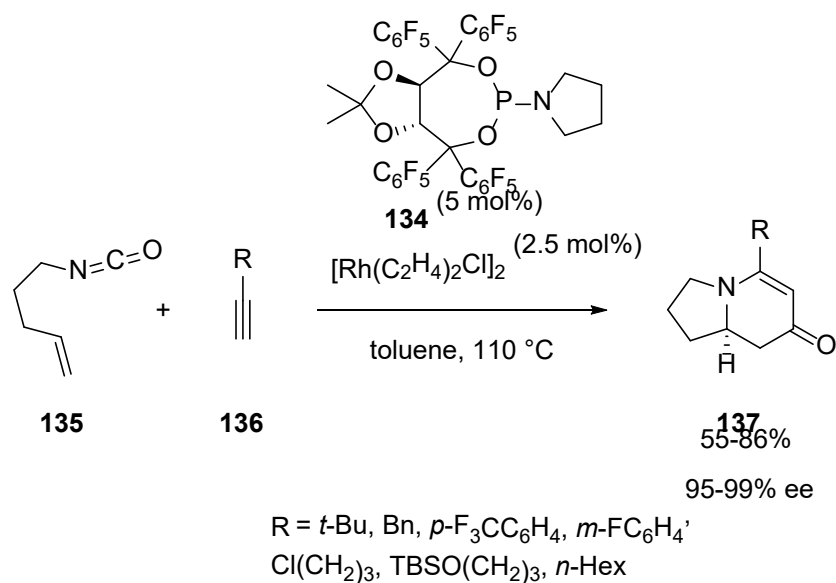
Scheme 47. Investigation of ligands in intramolecular [4+2] cycloaddition of triene **131a** [65].

The optimized reaction conditions involved the use of 6 or 10 mol% of a chiral catalyst generated from $[Rh(nbd)Cl]_2$, TADDOL-derived phosphite ligand **133** and $AgSbF_6$ at 50 °C in ethylacetate as the solvent (Scheme 48). This resulted in the intramolecular [4+2] cycloaddition of trienes **131** to afford the corresponding chiral hexahydroindene (X = C(CO₂Me)₂) and their hetero analogues **132** (X = O, NHTs) as single diastereomers in moderate to high yields (44-83%) and enantioselectivities (68-90% ee), as shown in Scheme 44.



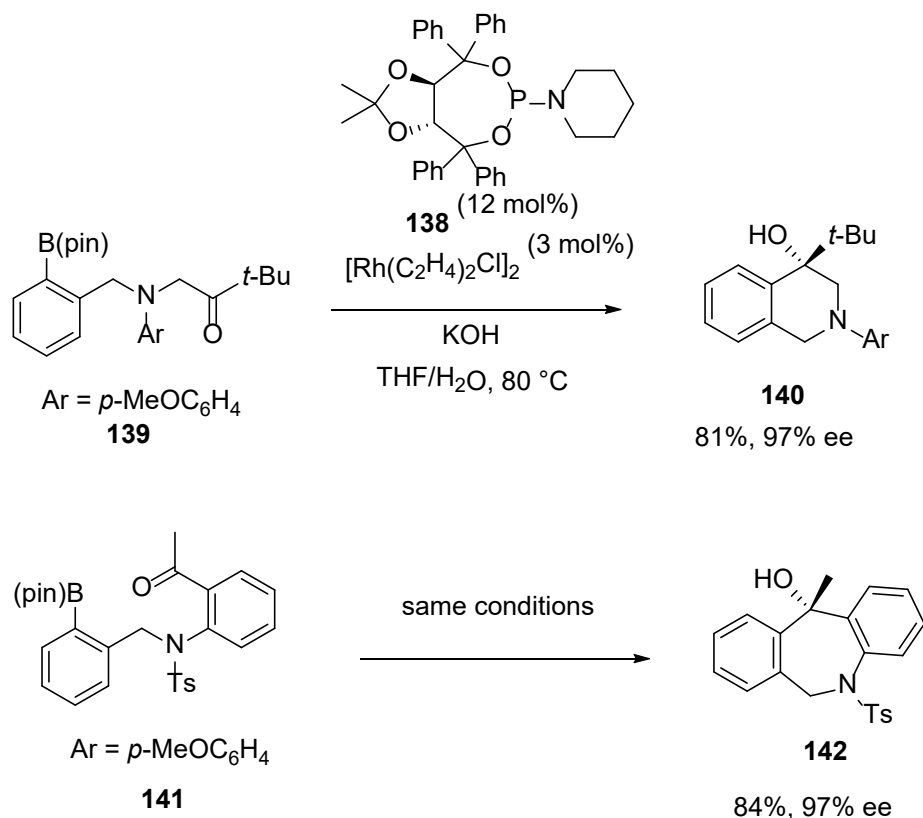
Scheme 48. Intramolecular [4+2] cycloaddition of trienes [65].

In 2013, perfluorinated TADDOL-based phosphoramidite **134** was demonstrated by Rovis et al. to be a highly enantioselective ligand for the chemoselective formation of chiral vinylogous amide cycloadducts **137** in the rhodium-catalyzed [2+2+2] cycloaddition of alkenyl isocyanates **135** with alkynes **136** [66]. As shown in Scheme 49, performing the reaction at 110 °C in toluene as the solvent in the presence of 5 mol% of ligand **134** combined with 2.5 mol% of $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ allowed a range of almost enantiopure (95-99% ee) indolizidinones **137** to be synthesized in good to high yields (55-86%). X-ray diffraction, NMR analysis, and DFT calculations revealed a shortened Rh–P bond and coordination of one C₆F₅ to the rhodium center via a weak Lewis acidic Z-type interaction, making the phosphoramidite a bidentate L,Z-ligand on rhodium.



Scheme 49. [2+2+2] Cycloaddition of alkenyl isocyanates with alkynes [66].

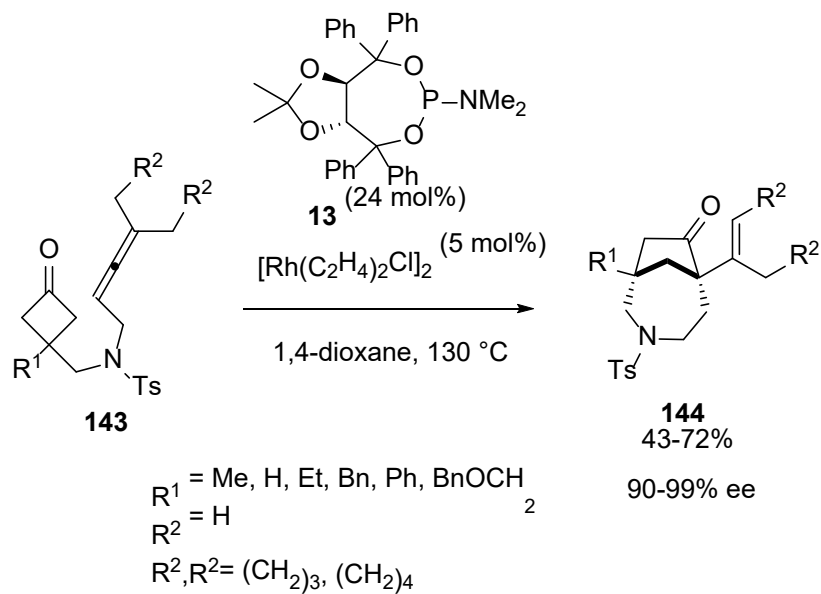
In the area of other cyclizations, Lam et al. reported in 2012 highly enantioselective rhodium-catalyzed cyclizations of arylboron compounds with ketones performed in the presence of 12 mol% of chiral phosphoramidite ligand **138** [67]. The cyclizations employed 3 mol% of $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ as the precatalyst and a 9:1 mixture of THF/H₂O as the solvent. For example, the reaction of substrate **139** containing an arylpinacolboronic ester tethered to a methyl ketone via a nitrogen linkage led upon heating at 80 °C to the corresponding almost enantiopure (97% ee) tetrahydroisoquino-lin-4-ol **140** in 81% yield (Scheme 50). The scope of the process was not limited to the production of six-membered azacycles since the cyclization of substrate **141** provided the corresponding enantiopure (97% ee) seven-membered dihydro-dibenzo[b,e]azepin-11-ol **142** in 84% yield (Scheme 50).



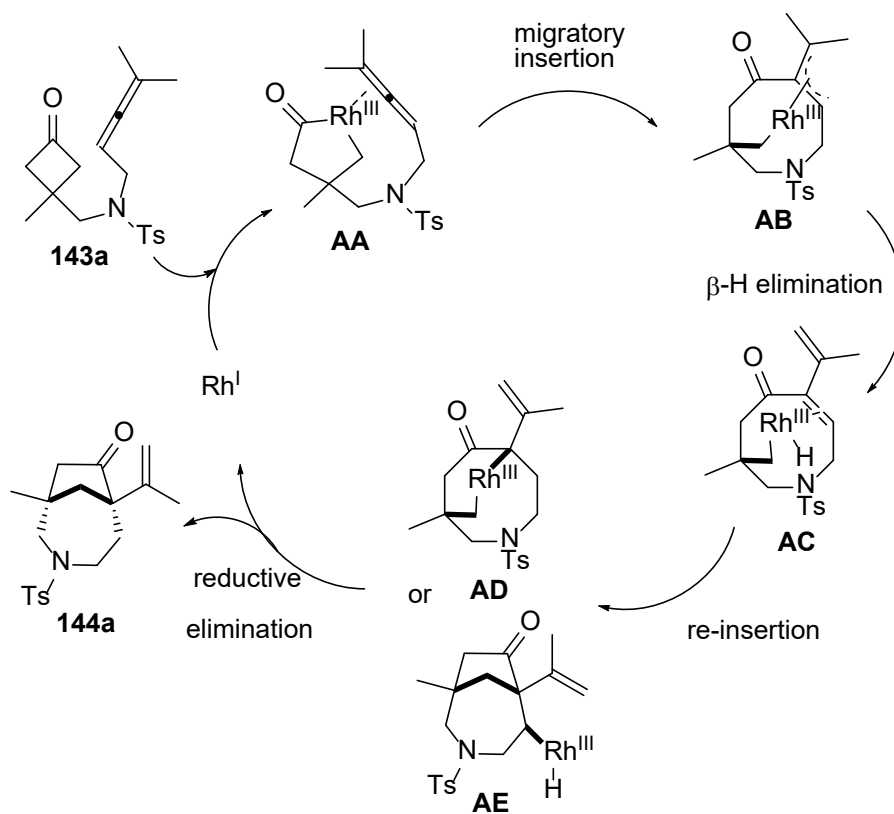
Scheme 50. Intramolecular cyclizations of arylboron compounds with ketones [67].

Later in 2015, Dong and Zhou developed an intramolecular enantioselective rhodium-catalyzed [4+1] cyclization occurring between cyclobutanones **143** and allenes [68]. Performed at 130 °C in 1,4-dioxane as the solvent and in the presence of 5 mol% of [Rh(C₂H₄)₂Cl]₂ combined with 24 mol% of chiral phosphoramidite ligand **13**, the cyclization afforded a range of chiral azepane-based scaffolds **144** containing two quaternary carbon stereocenters in moderate to good yields (43-72%) and uniformly excellent enantioselectivities (90-99% ee), as presented in Scheme 51. Remarkably, all the substrates bearing a hydrogen substitution at the C3 position (R² = H) provided the desired enantiopure products (99% ee). A mechanism is proposed in Scheme 51, showing that the reaction begins with the insertion of the Rh^I catalyst into the cyclobutanone α C–C bond to give five-membered rhodacycle **AA** with the allene group coordinated to the rhodium center. Then, a migratory insertion occurred to afford π allyl intermediate **AB**. The latter subsequently underwent a β-hydrogen elimination to give enone species **AC**. From intermediate **AC**, either a Rh–H or a Rh–C migratory insertion led to intermediates **AD** or **AE**, respectively. A final

reductive elimination of **AD/AE** resulted in the [4+1] product and regenerated the Rh^I catalyst.



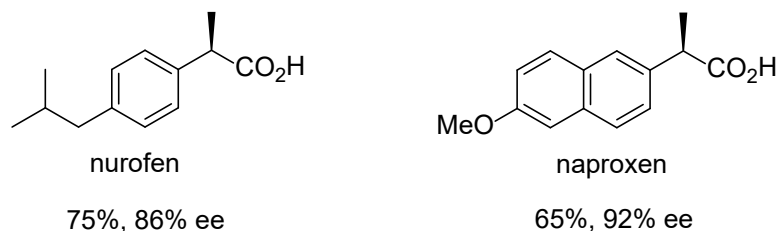
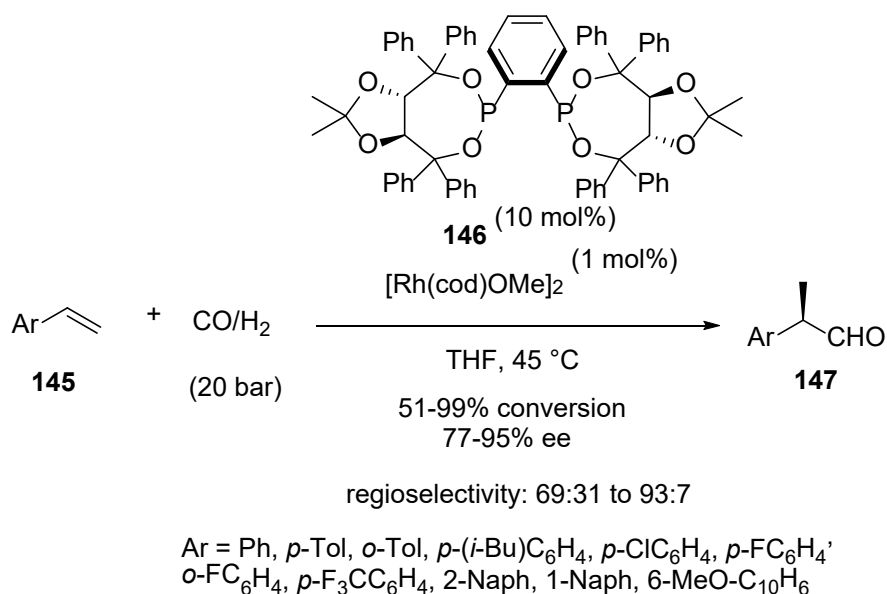
mechanism (with $\text{R}^1 = \text{Me, R}_2 = \text{H}$):



Scheme 51. Intramolecular [4+1] cyclization of cyclobutanones with allenes [68].

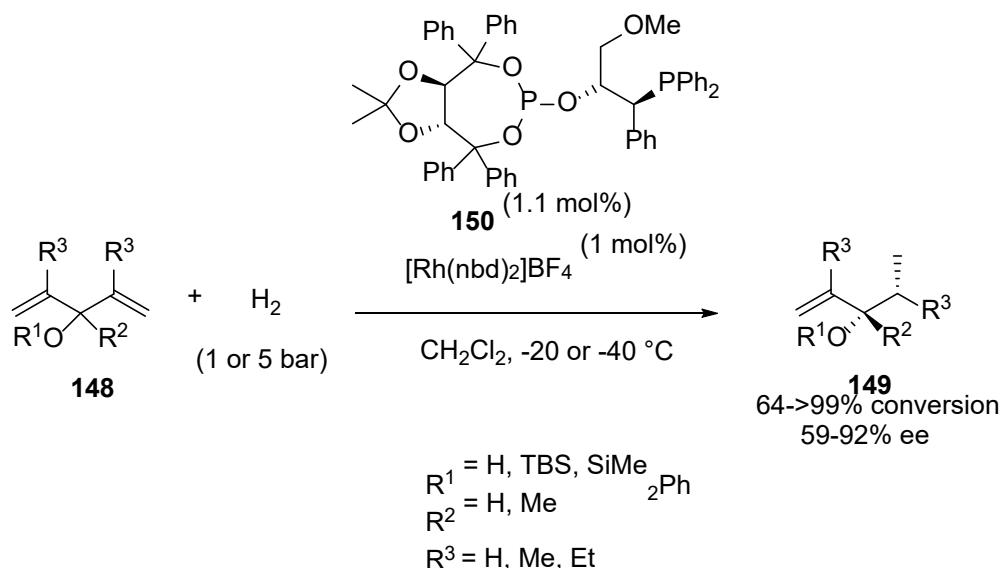
3.3. Miscellaneous reactions

In 2014, Burke et al. reported the first application of chiral rhodium catalysts prepared from TADDOL-derived phosphites in the enantioselective catalytic arylation of ethyl glyoxylate with organoboron reagents, providing access to chiral ethyl mandelate derivatives in variable yields (10-82%) and moderate enantioselectivities ($\leq 55\%$ ee) [69]. Later in 2015, Breit et al. described the synthesis of novel chiral bidentate bisphosphonite ligands derived from TADDOL to be evaluated in the asymmetric hydroformylation of styrene and derivatives **145** (Scheme 52) [70]. The use of optimal ligand **146** at 10 mol% of catalyst loading in combination with 1 mol% of $[\text{Rh}(\text{cod})\text{OMe}]_2$ as precatalyst in THF as the solvent at 45 °C allowed the asymmetric hydroformylation of aryl alkenes **145** under CO/H₂ pressure to provide the corresponding chiral aldehydes **147** with generally high conversions (51-99%), good to high regioselectivity (69:31 to 93:7) and homogeneously high enantioselectivities (77-95% ee). The utility of this novel methodology was demonstrated in the syntheses of anti-inflammatory drugs ibuprofen and naproxen starting from readily available *p*-isobutyl-styrene (Ar = *p*-(*i*-Bu)C₆H₄) and 6-methoxy-2-vinylnaphthalene (Ar = 6-MeOC₁₀H₆), respectively.



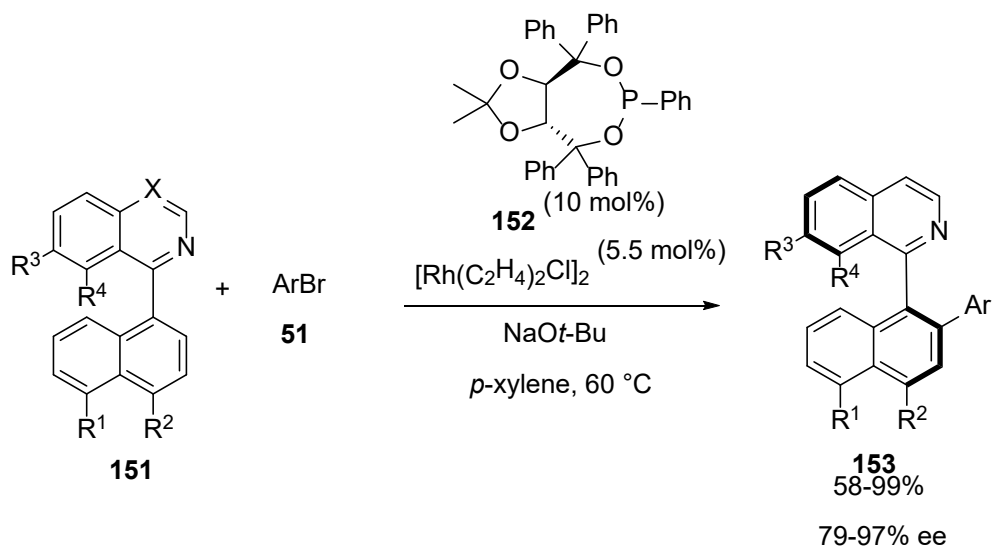
Scheme 52. Hydroformylation of styrene and derivatives [70].

In 2016, Vidal-Ferran et al. reported the rhodium-catalyzed hydrogenative desymmetrization of substituted 1,4-dienes **148** into the corresponding chiral secondary or tertiary alcohols or silylethers **149** [71]. As illustrated in Scheme 53, the hydrogenation was performed at -20 or -40 °C under H₂ pressure (1 or 5 bar) in dichloromethane as the solvent. The asymmetric induction arose from the use of a chiral rhodium catalyst derived from 1 mol% of [Rh(nbd)₂]BF₄ and 1.1 mol% of TADDOL-derived phosphite ligand **150**. It led with complete chemoselectivity and with generally complete conversion to chiral (protected) alcohols **149** in moderate to excellent enantioselectivities (59-92% ee). Moreover, the desymmetrization of a substrate containing two prostereogenic carbons (R¹ = R² = H, R³ = Et) proceeded with complete *syn*-diastereoselectivity.



Scheme 53. Hydrogenative desymmetrization of substituted 1,4-dienes [71].







In another context, You et al. developed in 2019 an enantioselective rhodium-catalyzed atroposelective C–H arylation of heterobiaryls **151** with (hetero)aryl bromides **51** (Scheme 54) [72]. The reaction was performed at 60 °C in *p*-xylene as the solvent in the presence of 10 mol% of chiral phosphonite ligand **152** combined with 5.5 mol% of $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ as precatalyst, delivering a range of chiral heterobiaryl products **153** in good to quantitative yields (58-99%) and high enantioselectivities (79-97% ee). Indeed, variously substituted 1-(naphthalen-1-yl)isoquinolines ($\text{X} = \text{CH}$) **151** reacted with a wide diversity of (hetero)aryl bromides **51** to give the corresponding chiral coupling products **153** in good to high yields (58-99%) and uniformly high ee values (79-97% ee). Remarkably, the reaction gave an excellent regioselective control for 4-(naphthalen-1-yl)-quinazoline ($\text{X} = \text{N}$), since the corresponding product was obtained in 95% yield and 86% ee. Furthermore, the scope of the methodology could be extended to aryl pyridine substrates **154**, affording the desired chiral products **155** in both excellent yields (91-99%) and enantioselectivities (91-94% ee), as shown in Scheme 54. In addition, 4-(naphthalen-1-yl)thieno[3,2-*c*]-pyridine ($\text{R}^1, \text{R}^2 = \text{S-CH=CH}$) was also compatible with the catalyst system, affording the corresponding product in both lower yield (71%) and enantioselectivity (81% ee).



X = CH, N

Ar = *p*-Tol, *p*-(*t*-Bu) C_6H_4 , *p*-MeOC C_6H_4 , *p*-(Me $_2$ N) C_6H_4 , Ph, *p*-FC C_6H_4 ,

p-ClC C_6H_4 , *p*-BrC C_6H_4 , *p*-F $_3$ CC C_6H_4 , *p*-NCC C_6H_4 , *m*-Tol, *m*-FC C_6H_4 , 3,5-Me $_2$ C C_6H_3 ,

2-Naph, , , , , , 

R 1 = H

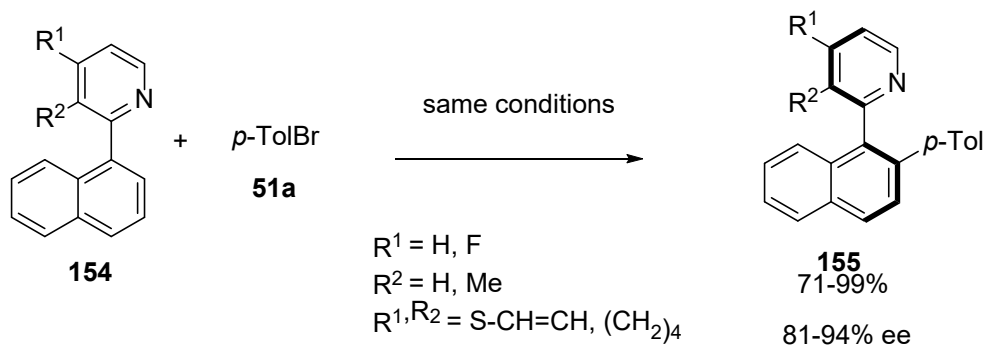
R 2 = H, F, Me, OMe

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

R 3 = H

R 4 = H

R $^3, \text{R}^4$ = (CH=CH) $_2$

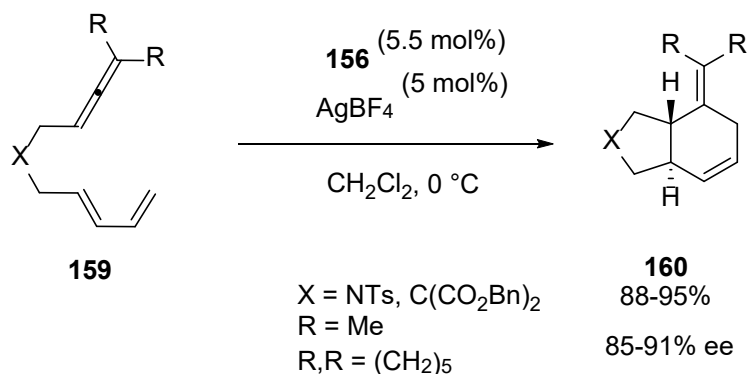
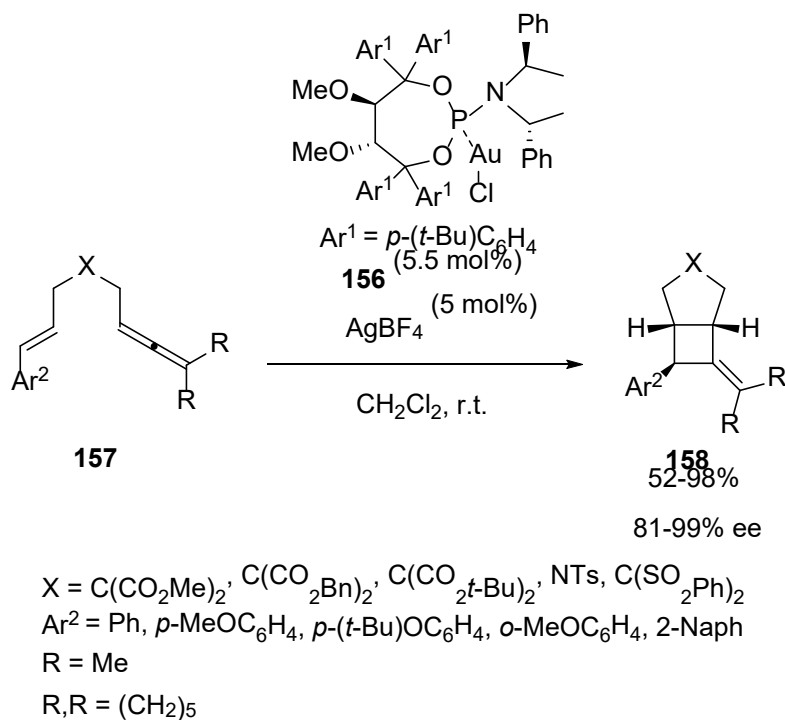


Scheme 54. Atroposelective C–H arylations of heterobiaryls with (hetero)aryl bromides [72].

4. Enantioselective gold-catalyzed reactions

4.1. Cycloadditions/cyclizations

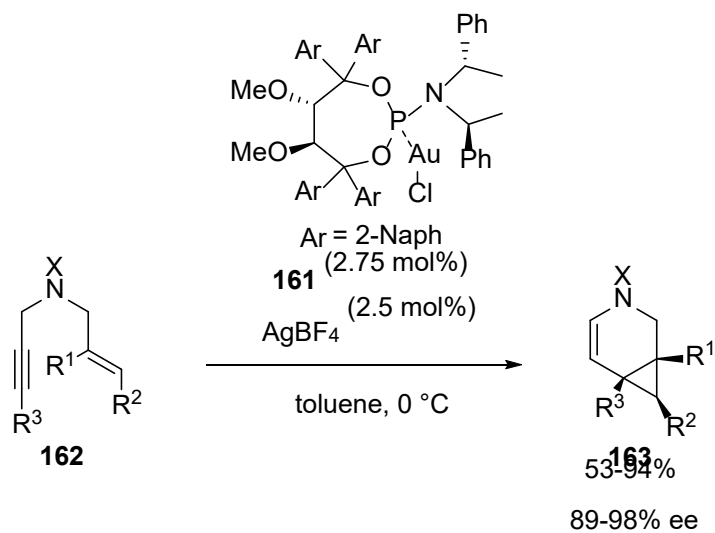
Gold catalysts play a unique role in homogeneous catalysis due to their high activity in activating π systems [73]. Especially, asymmetric gold catalysis [74] knows an intense development. In this area, Fürstner et al. demonstrated in 2012 that simple and economic TADDOL-derived phosphoramidites with an acyclic backbone were excellent ligands for asymmetric gold catalysis, allowing a number of different transformations to be performed with outstanding enantioselectivities [75]. The distinctive design element of this new family of ligands was their acyclic dimethylether backbone in lieu of the (isopropylidene) acetal moiety characteristic for traditional TADDOL derivatives. In a first time, preformed optimal novel phosphoramidite gold catalyst **156** was applied at 5.5 mol% of catalyst loading to promote an intramolecular asymmetric [2+2]-cycloaddition of ene-allenes **157**. Performed at room temperature in dichloromethane as the solvent, the cycloaddition led to the corresponding chiral bicyclic products **158** in moderate to quantitative yields (52-98%) and uniformly high enantioselectivities (81-99% ee), as shown in Scheme 55. Actually, in all cases of substrates, the reaction provided ee values higher than 95% excepted in the case of a bis-sulfone ($X = C(SO_2Ph)_2$) which gave the corresponding product in 81% ee. In a second time, the authors also used the same gold chiral complex **156** to promote the asymmetric intramolecular [4+2] cycloaddition of diene-allenes **159** (Scheme 55). As for the precedent [2+2] cycloadditions, the ligand with the acyclic backbone performed better than their relatives comprising a traditional TADDOL subunit. Indeed, the intramolecular [4+2] cycloaddition of diene-allenes **159** carried out in the presence of 5.5 mol% of chiral preformed catalyst **156** resulted in the formation of the corresponding chiral bicyclic products **160** in both excellent yields (88-95%) and enantioselectivities (85-91% ee).



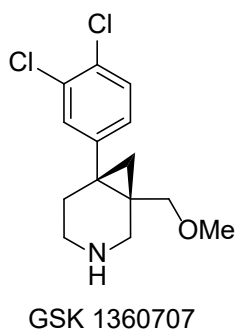
Scheme 55. Intramolecular [2+2] and [4+2] cycloadditions of ene-allenes and diene-allenes [75].

In the same report, a closely related chiral catalyst **161** was applied at 2.75 mol% of catalyst loading to promote one more type of asymmetric intramolecular cyclizations, such as the cycloisomerization of 1,6-enynes **162** into the corresponding chiral bicyclic products **163** achieved with moderate to excellent yields (53-94%) and homogeneously excellent enantioselectivities (89-98% ee), as illustrated in Scheme 56 [75]. In this case, the best results were obtained by performing the reaction at 0 °C in toluene as the solvent. The authors

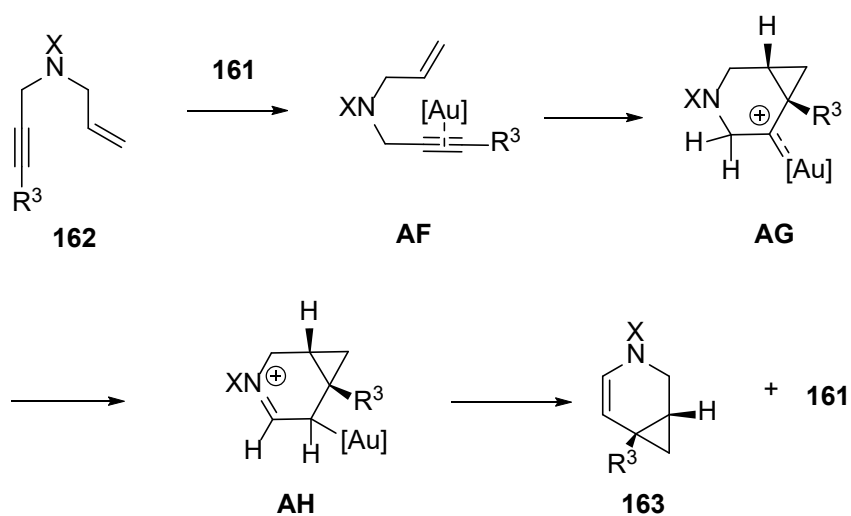
proposed the mechanism depicted in Scheme 56 which begins with the formation of gold complex **AF** through complexation of the gold chiral catalyst by the alkyne. Then, a concerted cyclopropanation occurs and delivers the carbenoid complex **AG**. The latter undergoes a 1,2-H-shift, resulting in the formation of intermediate **AH** which provides the final product and regenerates the chiral gold catalyst. The utility of this methodology was shown in an efficient synthesis of the antidepressive drug candidate GSK 1360707.



$X = \text{Cbz, Ts, SO}_2\text{Me, CO}_2\text{Me}$
 $R^1 = \text{H, Me, MeOCH}_2$
 $R^2 = \text{H, Ph}$
 $R^3 = \text{Ph, } p\text{-BrC}_6\text{H}_4, 3,4\text{-Cl}_2\text{C}_6\text{H}_3$

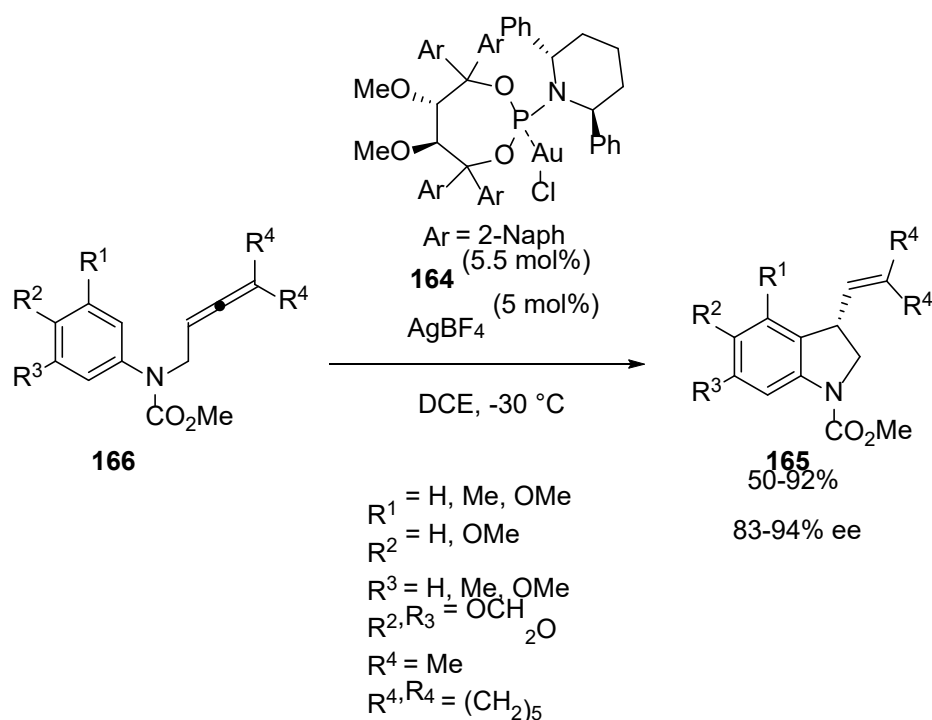


mechanism (with $R^1 = R^2 = \text{H}$):



Scheme 56. Cycloisomerization of 1,6-enynes [75].

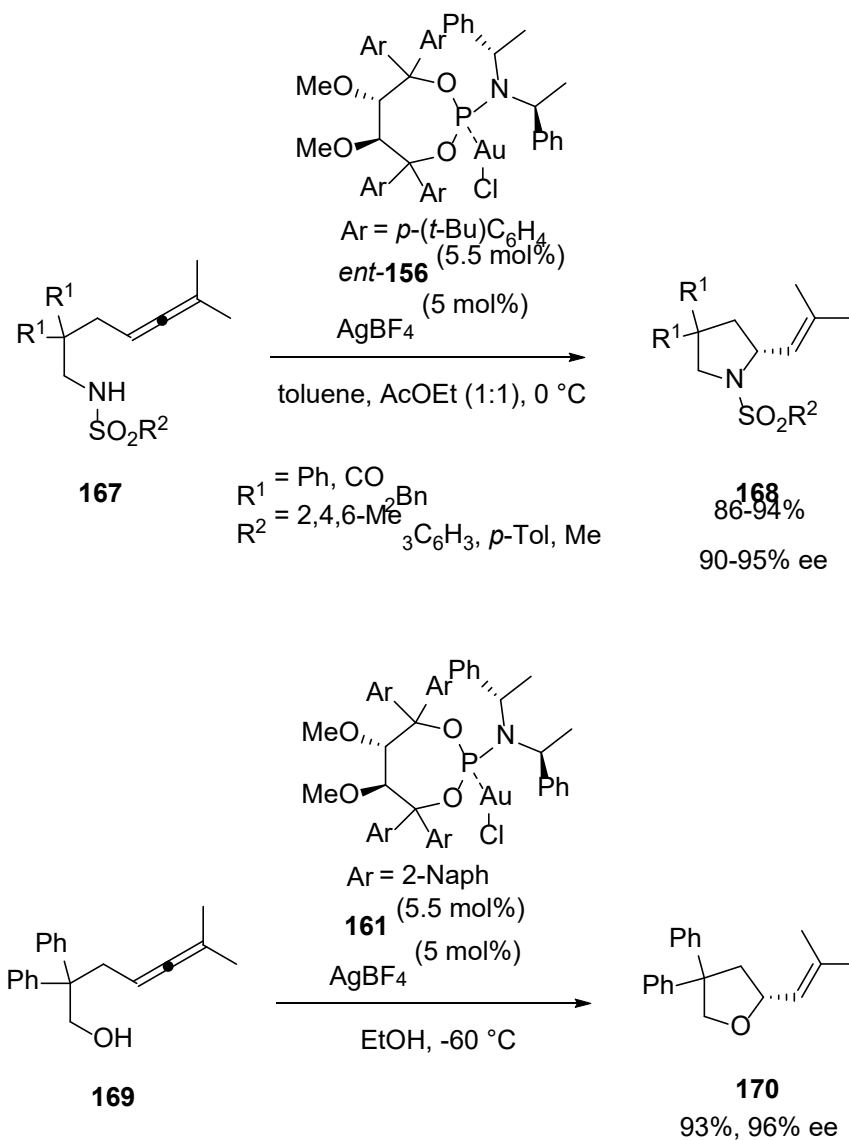
Another preformed TADDOL-derived phosphoramidite gold catalyst **164** also allowed indolines **165** to be accessed in high enantioselectivities (83-94% ee) and moderate to high yields (50-92%) from the asymmetric hydroarylation of the corresponding allenes **166** (Scheme 57) [75]. In this case, the reaction occurred at -30 °C in DCE as the solvent in the presence of 5.5 mol% of the gold complex.



Scheme 57. Hydroarylation of allenes [75].

An enantioselective gold-catalyzed intramolecular hydroamination of allenes was also achieved by the same authors in the presence of 5.5 mol% of catalyst *ent*-**156** [75]. As depicted in Scheme 58, a series of allenes **167** were effectively cyclized at 0 °C into the corresponding pyrrolidines **168** in a 1:1 mixture of toluene and ethyl acetate as the solvent with both excellent yields (86-94%) and ee values (90-95% ee). Furthermore, the authors still extended this chemistry to an intramolecular asymmetric hydroalkoxylation of allene **169**, which afforded at -60 °C the corresponding chiral tetrahydrofuran **170** with both excellent enantioselectivity (96% ee) and yield (93%) under catalysis with 5.5 mol% of gold complex

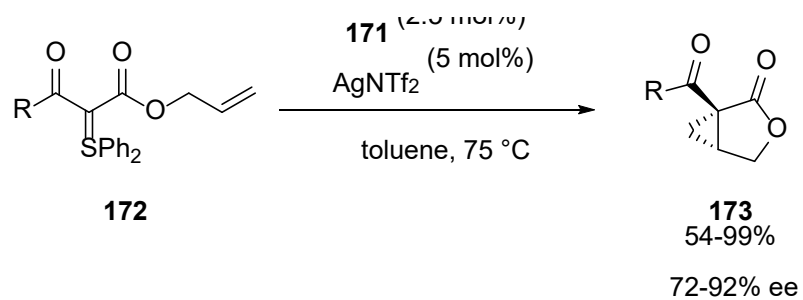
161. Somewhat surprisingly, the best result was obtained in ethanol as the solvent, which did not outperform the attack of the tethered OH group onto the allene moiety.



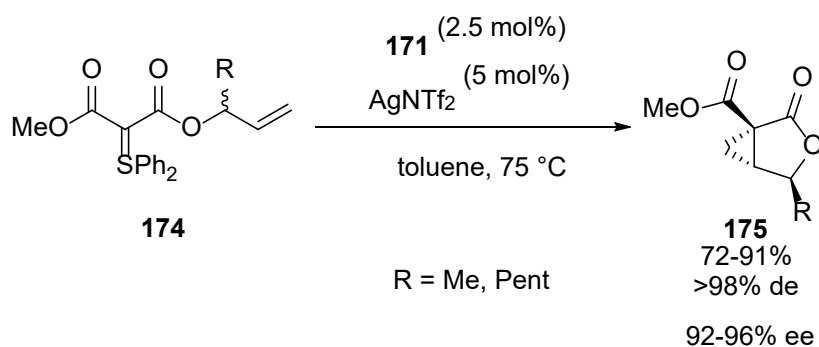
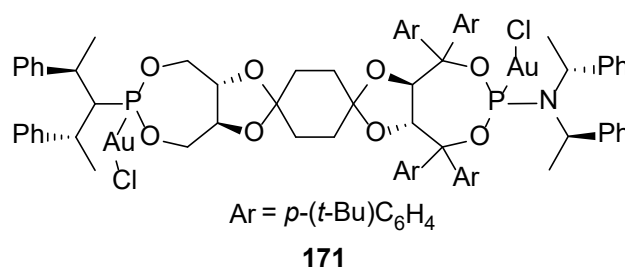
Scheme 58. Hydroamination and hydroalkoxylation of allenes [75].

In 2015, Maulide et al. developed an asymmetric intramolecular cyclopropanation of unactivated olefins with sulfonium ylides catalyzed by a preformed chiral bimetallic gold complex **171** derived from a TADDOL-phosphoramidite ligand [76]. In this novel catalyst, the two gold centers worked synergistically to enhance the enantioselectivity. Indeed, the key structural feature of the phosphoramidite ligand is the presence of two phosphorus donor

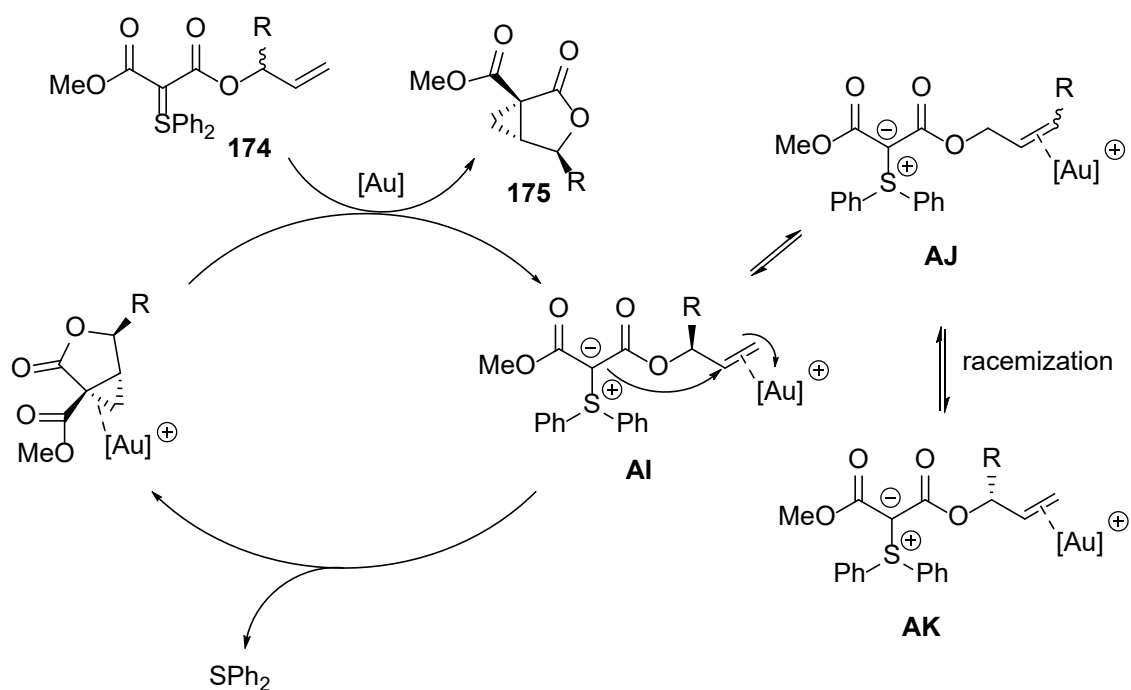
atoms which each coordinated to one gold center. As shown in scheme 59, in the presence of 2.5 mol% of this bimetallic catalyst, the reaction of sulfonium ylides **172** afforded the corresponding chiral cyclopropanes **173** in moderate to quantitative yields (54-99%) and good to high enantioselectivities (72-92% ee) when performed at 75 °C in toluene as the solvent. Moreover, the scope of the process was extended to racemic alkyl-substituted substrates **174** which led to the corresponding chiral cyclopropanes **175** as single diastereoisomers (>98% de), remarkable enantioselectivities (92-96% ee) combined with good yields (72-91%). This result suggested the possible occurrence of a dynamic deracemization process which is shown in the mechanism depicted in Scheme 59. Indeed, the substrate isomers could interconvert at a rate higher than that of the cyclopropanation reaction through an equilibrium between gold intermediates **AI**, **AJ** and **AK**. The gold catalyst further selected for the isomer carrying a terminal olefin appendage and effectively achieved highly enantioselective chiral recognition of only one enantiomer within the pair **AI/AK**, thereby cyclopropanating that stereoisomer with very high diastereoselection.



R = OEt, Oallyl, *i*-Pr, *i*-Bu, Me, Ph, *p*-MeOC₆H₄, *p*-Tol, *m*-Tol, *p*-PhC₆H₄, *p*-ClC₆H₄, 2-furyl, 2-thienyl

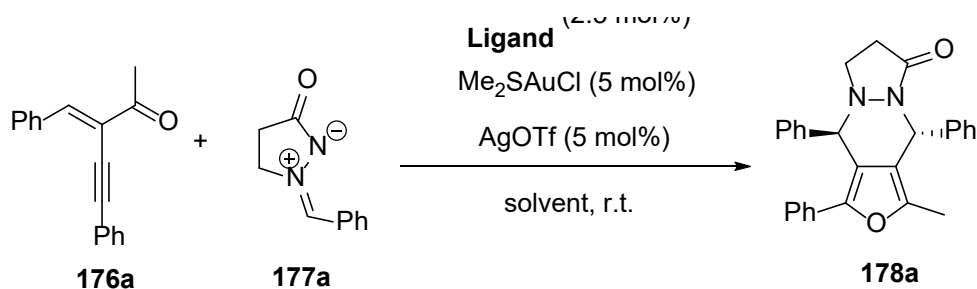


proposed mechanism:

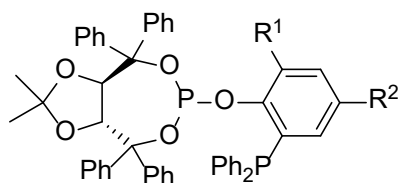


Scheme 59. Cyclopropanations of sulfonium ylides [76].

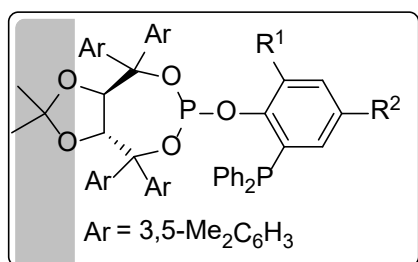
Pyridazines represent an important class of heterocycles exhibiting different biological activities. With the aim of developing a novel route to these molecules, Schmalz et al. investigated in 2018 an enantioselective gold-catalyzed reaction between 2-(1-alkynyl)-2-alken-1-ones **176** with azomethine imines **177** (Scheme 60) [77]. In a first time, established ligands, such as DIOP, BINAP, Josiphos, DTBM-Segphos, and phosphoramidites derived from 3,3'-disubstituted BINOLs, were investigated in combination with Me₂SAuCl as precatalyst to promote the domino cyclization/[3+3] cycloaddition reaction between **176a** and **177a** but the corresponding product **178a** was obtained with low enantioselectivities ($\leq 34\%$ ee). Then, the authors tested TADDOL-based phosphite ligands **L1-L10** which were found to react smoothly at room temperature in dichloromethane or acetonitrile as solvent. Interestingly, the use of the most sterically hindered ligands **L6** and **L8** allowed cycloadduct **178a** to be synthesized in good yields (65-71%) and moderate enantioselectivities (49% and 54% ee, respectively) when the reaction was performed in dichloromethane as solvent while ligand **L1** with a small methyl substituent in R¹ position only gave 18% ee. Employing optimal ligands **L6** and **L8** in acetonitrile as solvent allowed to improve both the yields (68-79%) and enantioselectivities (61-67% ee). In order to increase the enantioselectivity of the reaction, five additional and even bulkier phosphite ligands **179** and **L11-L14** derived from a TADDOL exhibiting 3,5-dimethylphenyl substituents instead of the common phenyl units were synthesized by the authors. The investigation of ligands **179** and **L11-L14** in the reaction of **176a** with **177a** under the improved conditions revealed that the structural modification of the TADDOL unit led indeed to significant changes in the reaction outcome. The substitution pattern of the ligand backbone again had a pronounced effect on the ligand performance. In this case, ligand **179** with an isopropyl group in R¹ position gave better results (85% yield, 83% ee) than ligands **L11-L14** with a bulkier R¹ substituent (69-76% yields, 58-72% ee).



with ligands:



- L1:** R₁ = Me, R₂ = H: 32%, 18% ee in CH₂Cl₂
L2: R₁ = Et, R₂ = H: 35%, 23% ee in CH₂Cl₂
L3: R₁ = *i*-Pr, R₂ = H: 48%, 32% ee in CH₂Cl₂
L4: R₁ = Ph, R₂ = H: 43%, 21% ee in CH₂Cl₂
L5: R₁ = *t*-Bu, R₂ = H: 49%, 42% ee in CH₂Cl₂
L6: R₁ = R₂ = *t*-Bu: 65%, 49% ee in CH₂Cl₂
 and 68%, 61% ee in MeCN
L7: R₁ = R₂ = *t*-Pent: 39%, 19% ee in CH₂Cl₂
L8: R₁ = *t*-Pent, R₂ = H: 71%, 54% ee in CH₂Cl₂
 and 79%, 67% ee in MeCN
L9: R₁ = *t*-Bu, R₂ = OMe: 52%, 47% ee in CH₂Cl₂
L10: R₁ = Pr, R₂ = H: 49%, 51% ee in CH₂Cl₂

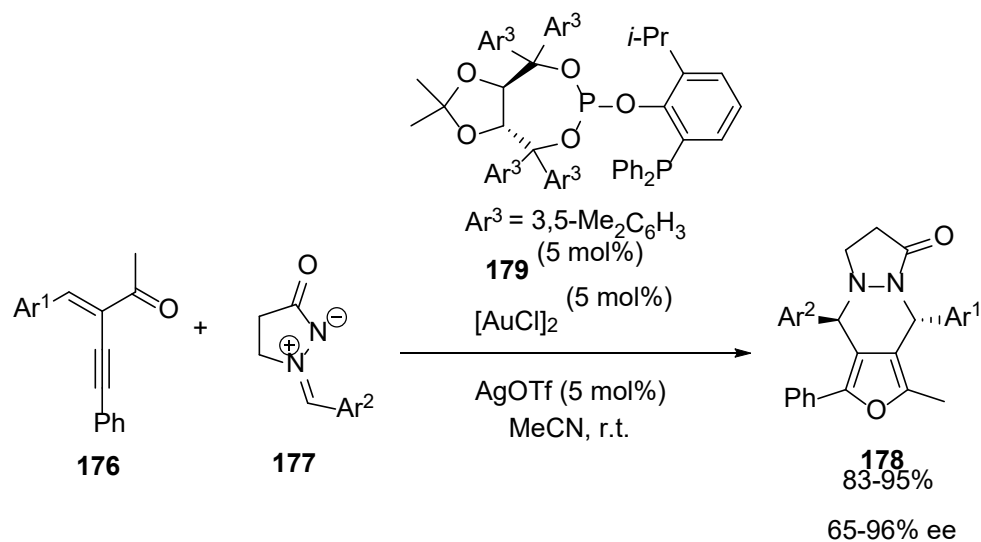


- L19:** R₁ = *i*-Pr, R₂ = H: 85%, 83% ee in MeCN
L11: R₁ = Ph, R₂ = H: 76%, 59% ee in MeCN
L12: R₁ = R₂ = *t*-Bu: 71%, 69% ee in MeCN
L13: R₁ = *t*-Pent, R₂ = H: 69%, 58% ee in MeCN
L14: R₁ = R₂ = *t*-Pent: 70%, 72% ee in MeCN

Scheme 60. Investigation of ligands in domino cyclization/[3+3] cycloaddition reaction of 2-(1-alkynyl)-2-alken-1-one **176a** with azomethine imine **177a** [77].

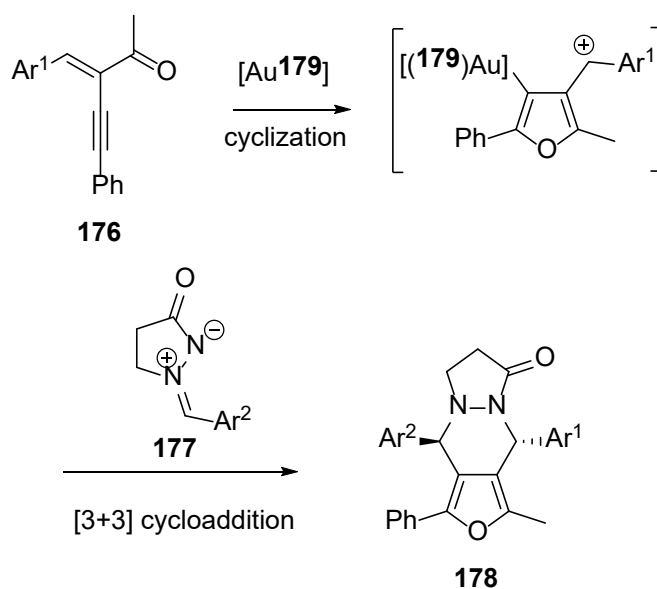
Having established phosphite **179** as optimal ligand, the authors optimized the reaction conditions for the domino cyclization/[3+3] cycloaddition reaction between 2-(1-alkynyl)-2-alken-1-ones **176** and azomethine imines **177**. These involved the use of 5 mol% of [AuCl]₂ as precatalyst, and the same quantity of chiral phosphite ligand **179** at room temperature in acetonitrile as the solvent, which resulted in the regio- and diastereoselective formation of chiral substituted furo[3,4-d]-tetrahydropyridazines derivatives **178** with high yields (83-95%) and moderate to high enantioselectivities (65-96% ee). As shown in Scheme 61, the process evolved through a domino cyclization/[3+3] cycloaddition reaction. It must be noted that his

work represented the first example of a simultaneous construction of a furan and a hydroxyridazine ring in a single synthetic operation.



$\text{Ar}^1 = \text{Ph}, p\text{-MeOC}_6\text{H}_4$
 $\text{Ar}^2 = \text{Ph}, p\text{-MeOC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-O}_2\text{NC}_6\text{H}_4, p\text{-Tol}, p\text{-}(t\text{-Bu})\text{C}_6\text{H}_4, p\text{-NCC}_6\text{H}_4, m\text{-MeOC}_6\text{H}_4, o\text{-MeOC}_6\text{H}_4, m\text{-O}_2\text{NC}_6\text{H}_4, o\text{-ClC}_6\text{H}_4, 2\text{-furyl}, 5\text{-Me-2-furyl}$

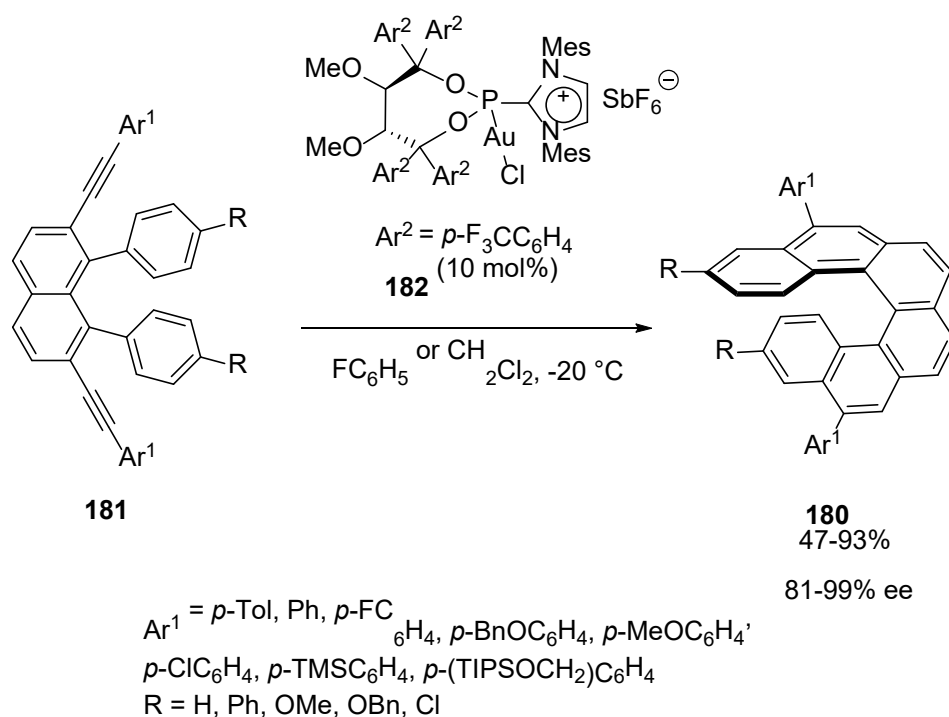
mechanism:



Scheme 61. Domino cyclization/[3+3] cycloaddition reaction of 2-(1-alkynyl)-2-alken-1-ones with azomethine imines [77].

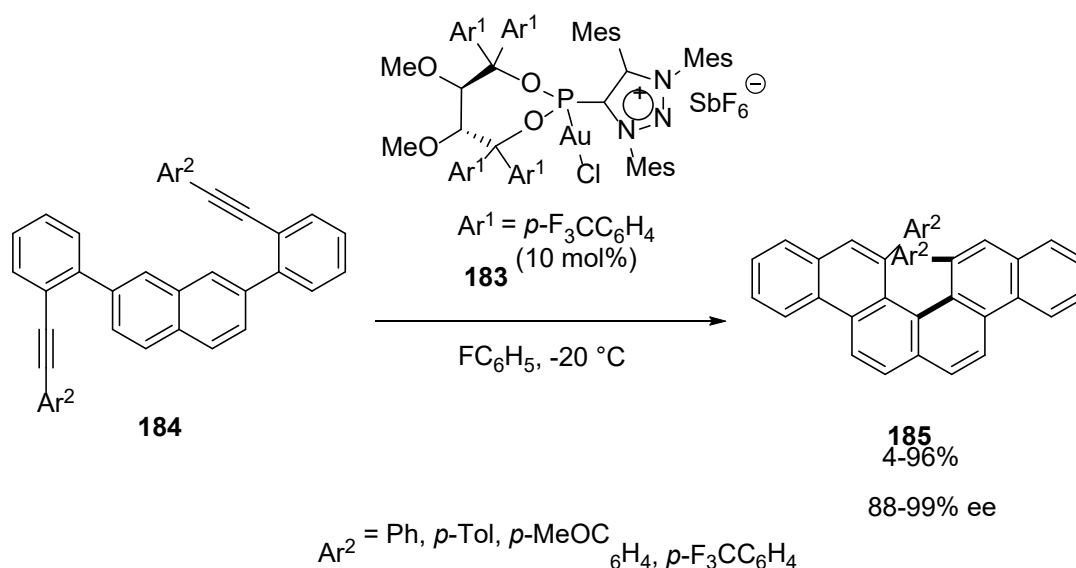
4.2. C-H Functionalizations

In 2017, a highly regio- and enantioselective synthesis of substituted [6]carbohelicenes **180** was reported by Alcarazo et al. on the basis of a sequential intramolecular gold-catalyzed hydroarylation of diynes **181** employing newly designed chiral cationic phosphinites derived from TADDOL as ancillary ligands [78]. As illustrated in Scheme 62, in the presence of 10 mol% of preformed chiral catalyst **182** derived from one of these ligands, diynes **181** underwent asymmetric hydroarylation to give the corresponding chiral substituted [6]helicenes **180** in variable yields (47-93%) and uniformly high enantioselectivities (81-99% ee). Later in 2018, the same authors even extended the scope of this methodology [79], making this type of complexes the most efficient catalysts for this kind of enantioselective transformation. The positively charged imidazolium group directly attached to phosphorus was found responsible for the enhancement of Lewis acidity at the metal center in comparison with traditional catalysts.



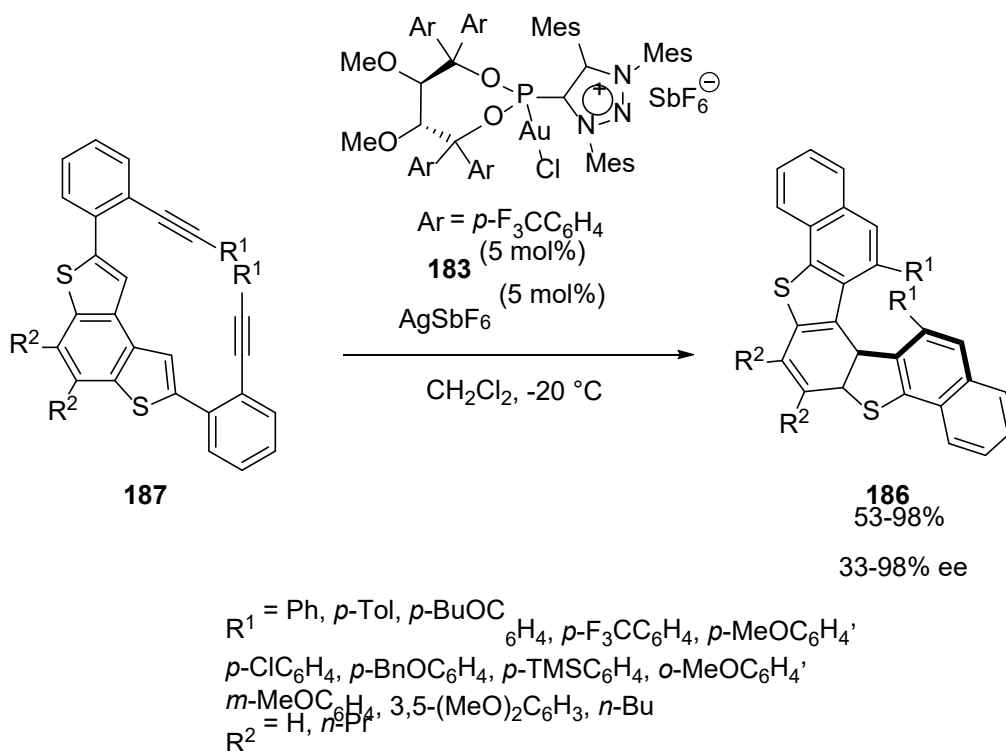
Scheme 62. Intramolecular hydroarylation of diynes [78].

In 2020, a closely related chiral gold catalyst **183** was applied by the same authors to promote a related enantioselective intramolecular hydroarylation of diynes **184** [80]. Performed with 10 mol% of this preformed catalyst, the reaction afforded the corresponding chiral 1,12-disubstituted[4]helicenes **185** in low to quantitative yields (4-96%) and uniformly excellent enantioselectivities (88-99% ee), as shown in Scheme 63. In general, the yields were good (57-96%) excepted for the reaction of a substrate bearing a strong electron-withdrawing substituent ($\text{Ar}^2 = p\text{-CF}_3\text{C}_6\text{H}_4$) which led to only traces (4% yield) of the desired albeit enantiopure [4]helicene (95% ee).



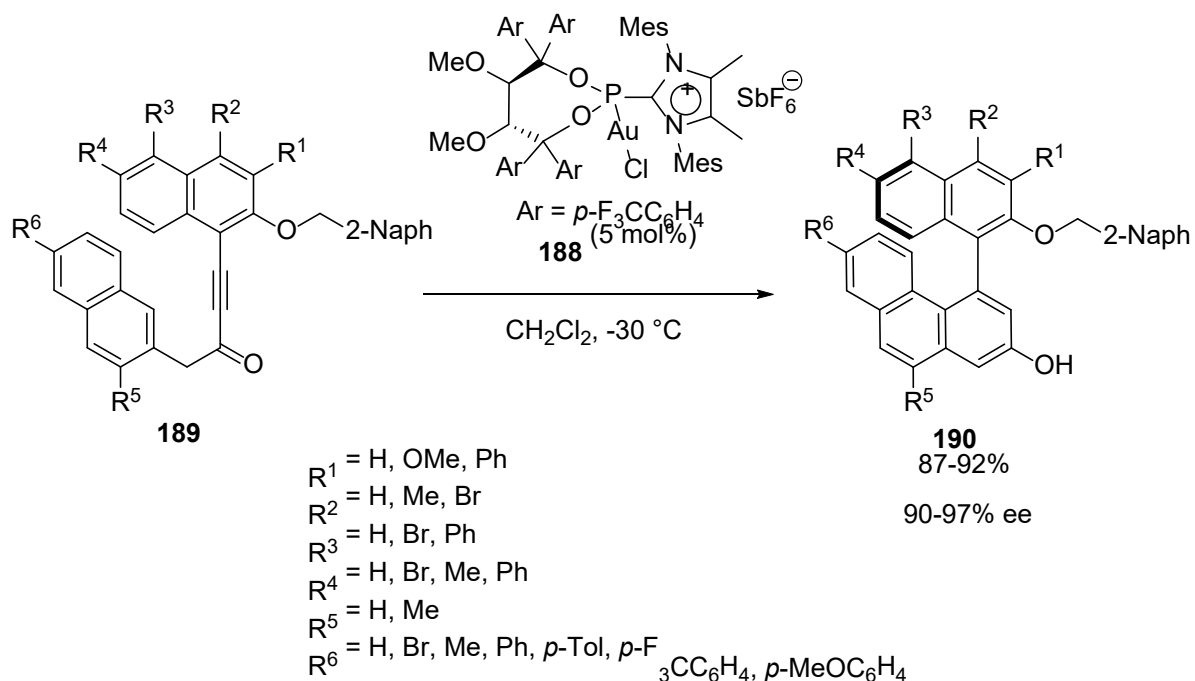
Scheme 63. Intramolecular hydroarylation of other diynes [80].

In 2022, the same catalyst **183** was applied by Alcarazo and Cauteruccio to promote the first highly enantioselective synthesis of dithiahelicenes **186**, through related asymmetric gold-catalyzed intramolecular hydroarylation of corresponding alkynes **187** [81]. In this case, the reaction was performed at $-20\text{ }^\circ\text{C}$ in dichloromethane as the solvent in the presence of only 5 mol% of catalyst **183**, allowing the synthesis of a range of differently substituted chiral dithiahelicenes **186** with moderate to excellent yields (53-98%) and enantioselectivities (33-98% ee), as presented in Scheme 64.



Scheme 64. Intramolecular hydroarylation of other diynes [81].

In addition, the same group earlier developed a highly atroposelective synthesis of 1,1'-binaphthalene-2,3'-diols on the basis of an enantioselective gold-catalyzed intramolecular hydroarylation of appropriately designed naphthols [82]. In this case, 5 mol% of another preformed TADDOL-derived catalyst **188** was employed at $-30\text{ }^\circ\text{C}$ in dichloromethane as the solvent to promote the intramolecular hydroarylation of variously substituted naphthols **189** into the corresponding chiral binaphthols **190** which were obtained in both excellent yields (87-92%) and enantioselectivities (90-97% ee), as shown in Scheme 65. The authors demonstrated that the use of a 3,4-disubstituted imidazolium unit directly attached to the phosphorus atom of the ancillary ligand, and 2-naphthalenemethyl moieties as protecting group at the naphthol substrates **189** were found to be essential to achieve high enantioselectivities.



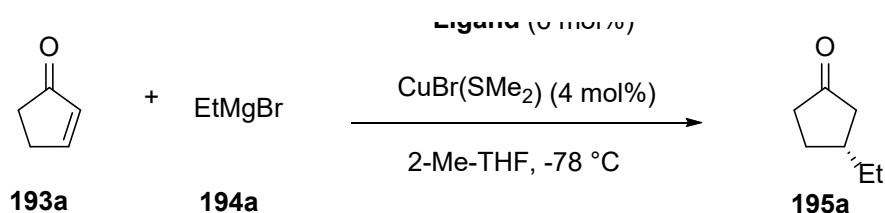
Scheme 65. Intramolecular hydroarylation of naphthols [82].

5. Enantioselective copper-catalyzed reactions

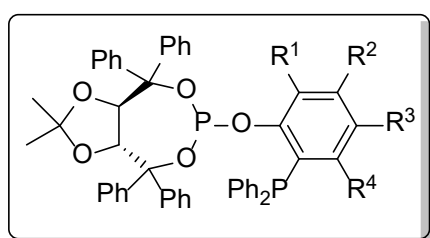
5.1. Michael reactions

In comparison with other transition metals, copper presents the advantages to be more abundant, cheaper and lower toxic. In this context, more ecologic and economic enantioselective reactions have been developed in the last decade on the basis of asymmetric copper catalysis. Among them, are asymmetric copper-catalyzed conjugate additions of organometallic reagents to α,β -unsaturated acceptors, representing fundamental transformations in organic synthesis [83]. As an example using TADDOL-derived phosphorus ligands, Schmalz et al. investigated in 2011 enantioselective copper-catalyzed conjugate additions of Grignard reagents to different cyclic α,β -unsaturated carbonyl compounds [84]. These reactions were performed at $-78\text{ }^\circ\text{C}$ upon catalysis with 4 mol% of $\text{CuBr}(\text{SMe}_2)$ as precatalyst and 6 mol% of a chiral phosphite ligand in 2-Me-THF as the solvent. Different types of chiral phosphite ligands were investigated in the Michael addition

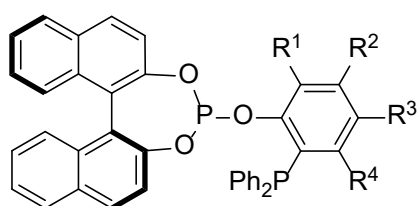
of EtMgBr **194a** to cyclopentenone **193a** (Scheme 66). Among TADDOL-derived ligands, phosphites **191** and **192** bearing a bulky *t*-butyl group at the *ortho*-position to the phosphite moiety, were found optimal, affording the Michael product **195a** with high enantioselectivity (90% ee). The conversion was slightly higher in the case of ligand **191** in comparison with ligand **192** (98% vs 91%). Other TADDOL-derived ligands **L1-L4** exhibiting less sterically hindered substituents (R^1) at the *ortho*-position of the phosphite moiety as well as BINOL-derived ligands **L5-L10** were also investigated but all resulted in much lower enantioselectivities (5-55% ee).



with ligands:



- 191:** $R^1 = t\text{-Bu}$, $R^2 = R_3 = R_4 = \text{H}$: 98%, 90% ee
192: $R^1 = R^3 = t\text{-Bu}$, $R_2 = R_4 = \text{H}$: 91%, 90% ee
L1: $R^1 = \text{Ph}$, $R^2 = R_3 = R_4 = \text{H}$: 93%, 15% ee
L2: $R^1 = i\text{-Pr}$, $R^2 = R_3 = R_4 = \text{H}$: 93%, 37% ee
L3: $R^1 = R^4 = \text{Me}$, $R_2 = R_3 = \text{H}$: 94%, 11% ee
L4: $R^1 = \text{Me}$, $R^2 = R_3 = R_4 = \text{H}$: 92%, 11% ee

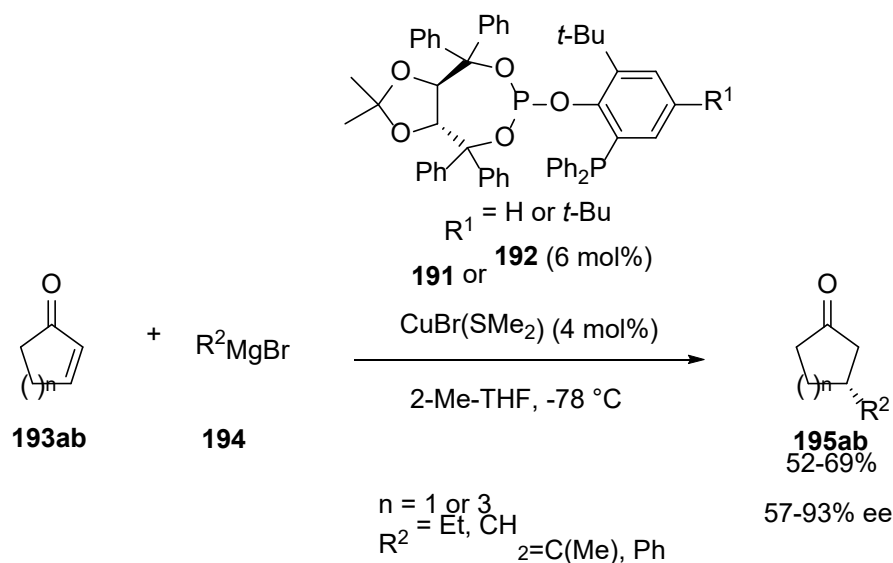


- L5:** $R^1 = R^2 = \text{Me}$, $R_3 = R_4 = \text{H}$: 94%, 7% ee
L6: $R^1 = i\text{-Pr}$, $R^2 = R_3 = \text{H}$, $R_4 = \text{Me}$: 95%, 5% ee
L7: $R^1 = R^2 = R_3 = R_4 = \text{H}$: 94%, 55% ee
L8: $R^1 = \text{Ph}$, $R^2 = R_3 = R_4 = \text{H}$: 96%, 37% ee
L9: $R^1 = i\text{-Pr}$, $R^2 = R_3 = R_4 = \text{H}$: 97%, 5% ee
L10: $R^1 = \text{Me}$, $R^2 = R_3 = R_4 = \text{H}$: 96%, 15% ee

Scheme 66. Investigation of ligands in Michael addition of EtMgBr to cyclopentenone [84].

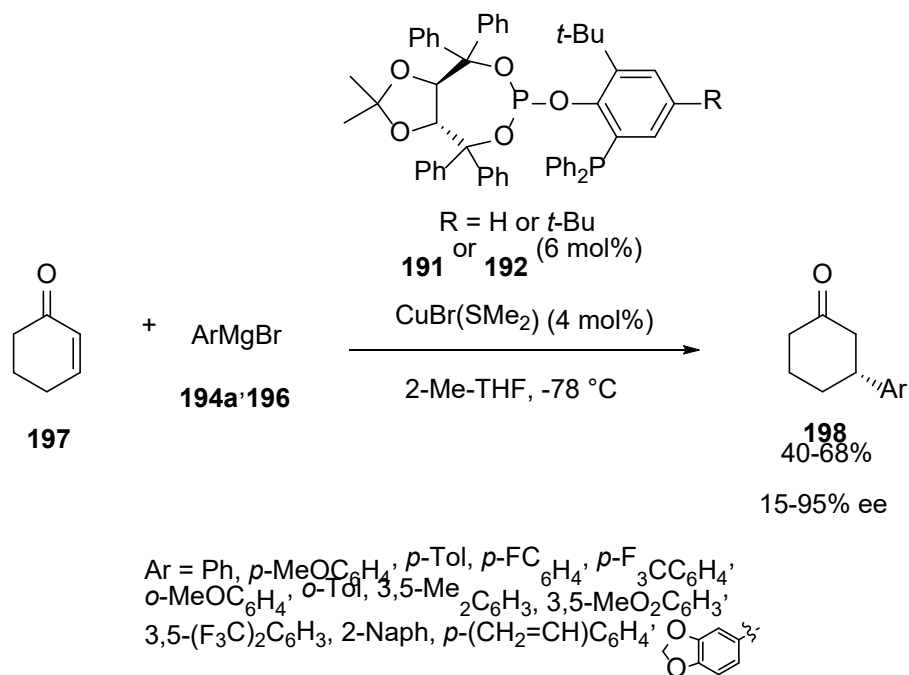
In the presence of optimal chiral phosphite ligands **191** ($R^1 = \text{H}$) or **192** ($R^1 = t\text{-Bu}$), the authors extended the scope of the reaction of cyclopentenone **193a** ($n = 1$) as well as

cycloheptenone **193b** ($n = 3$) with several Grignard reagents **194** to afford the corresponding chiral Michael products **195ab** which were obtained with moderate to good yields (52-69%) and moderate to high enantioselectivities (57-93% ee), as presented in Scheme 67. In addition to alkyl Grignard reagents, alkenyl and aryl Grignard reagents could be employed as well.



Scheme 67. Michael addition of Grignard reagents to cyclopentenone and cycloheptenone [84].

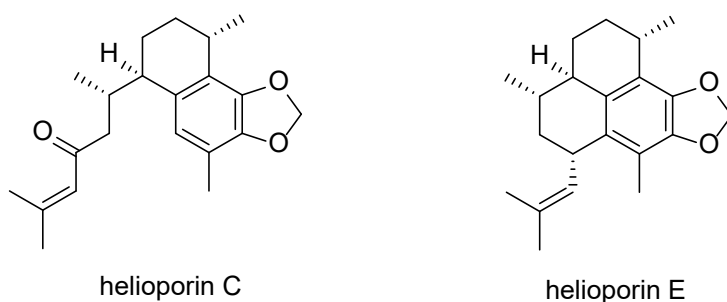
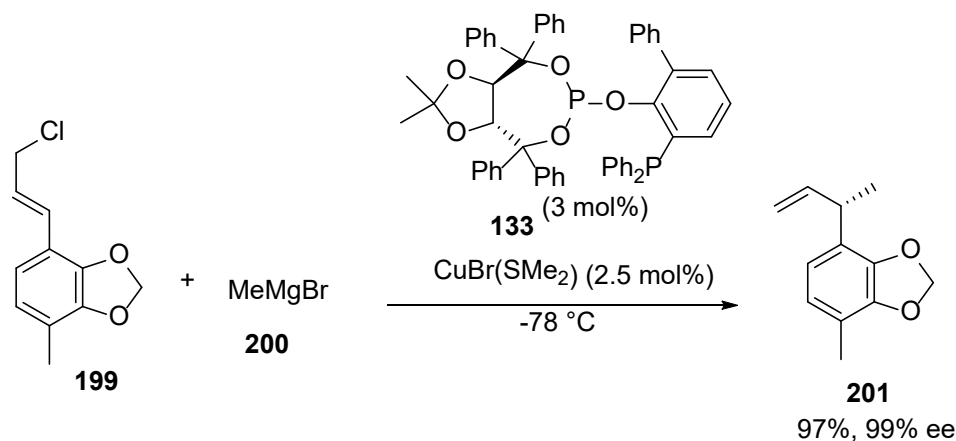
Later in 2012, the same group investigated the performance of the same TADDOL-based phosphite ligands **191** and **192** in enantioselective conjugate additions of aryl Grignard reagents **194a,196** to challenging cyclohexanone **197** (Scheme 68) [85]. Under the same reaction conditions, this resulted in the formation of a series of chiral 3-arylcyclohexanones **198** with moderate yields (40-68%) and low to excellent ee values (15-95% ee). The catalyst system tolerated the presence of different substituents on the phenyl ring of the Grignard reagents. It was found that electron-donating substituents in *para*- or *meta*-positions gave the best enantioselectivities, whereas fluoro- and CF_3 -substituted aryl-Grignard reagents provided low ee values (13-15% ee).



Scheme 68. Michael addition of aryl Grignard reagents to cyclohexenone [85].

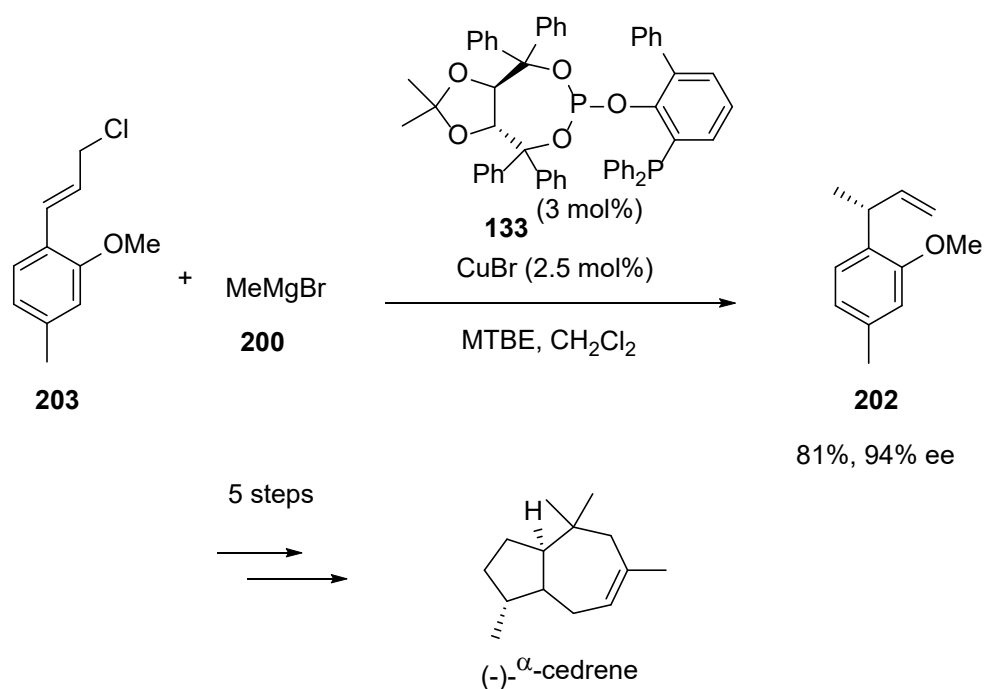
5.2. Allylic alkylations

In 2012, a short and total synthesis of helioporins C and E, which are bioactive marine diterpenes containing a serrulatane or amphilectane skeleton, was elaborated by Schmalz et al. [86]. The key step of this synthesis consisted in an enantioselective copper-catalyzed allylic alkylation of cinnamyl chloride **199** with methylmagnesium bromide **200** performed in the presence of chiral TADDOL-based phosphite ligand **133** (Scheme 69). The allylic methylation occurred at $-78\text{ }^\circ\text{C}$ in the presence of 3 mol% of this ligand in combination with 2.5 mol% of $\text{CuBr(SMe}_2\text{)}$ as precatalyst, affording the desired enantiopure (99% ee) product **201** in 97% yield. The latter was further converted into helioporins C and E through ten supplementary steps.



Scheme 69. Allylic methylation of a cinnamyl chloride with methylmagnesium bromide and synthesis of helioporins C and E [86].

In 2017, the same authors revisited the Wender cedrene synthesis [87] by introducing a related catalytic enantioselective entry to the chiral key intermediate **202** [88]. As illustrated in Scheme 70, the asymmetric copper-catalyzed allylic methylation of cinnamyl chloride **203** with methylmagnesium bromide **200** promoted by 2.5 mol% of CuBr and 3 mol% of the same phosphite ligand **133** furnished the desired key chiral intermediate **202** in 81% yield and 94% ee. The latter was then converted into expected (-)- α -cedrene through five supplementary steps.

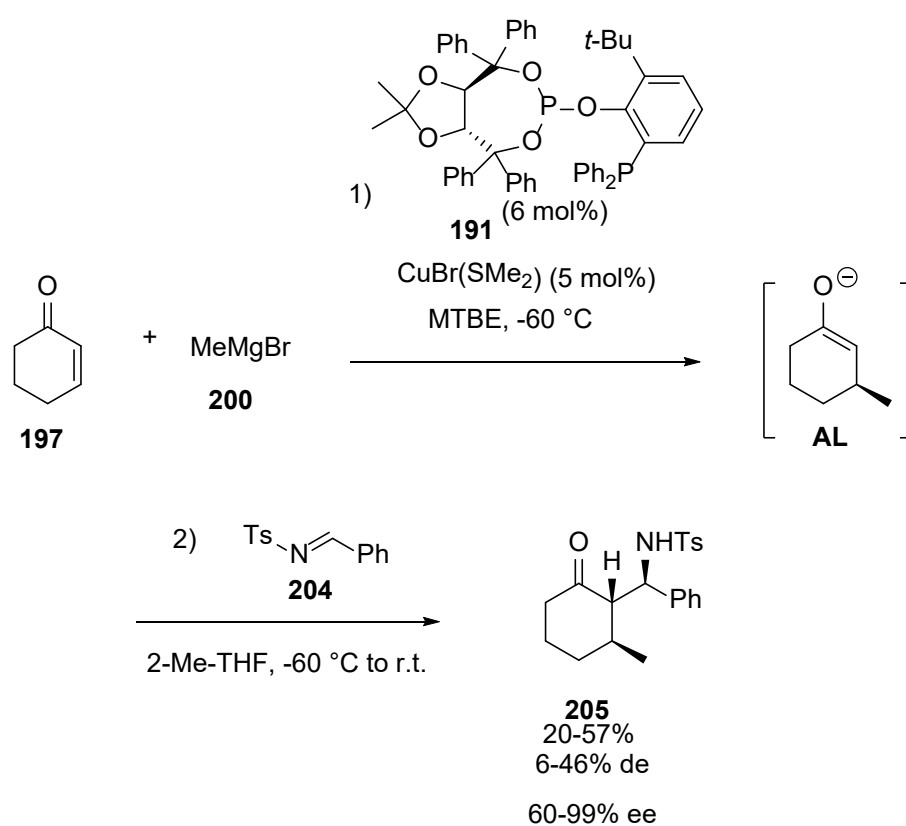


Scheme 70. Allylic methylation of another cinnamyl chloride with methylmagnesium bromide and synthesis of (-)- α -cedrene [88].

5.3. Domino and tandem reactions

Domino reactions, which avoid the isolation and purification of intermediates and costly protection-deprotection processes, have become essential economic processes to rapidly reach highly complex chiral important products [89]. In the last decade, more ecologic and economic enantioselective domino reactions have been catalyzed by chiral copper catalysts [89z]. As an example, Sebesta et al. demonstrated in 2012 that the chiral enolate species **AL**, resulting from the conjugate addition of methylmagnesium bromide **200** to cyclohexenone **197** performed in the presence of a chiral copper catalyst derived from phosphite ligand **191**, could be trapped with *N*-tosylimine **204** [90]. Inspired by the work from Schmalz et al. [85], dealing with copper-catalyzed asymmetric conjugate addition of aryl Grignard reagents to cyclohexenone promoted by the same phosphite ligand **191**, a tandem Michael/Mannich-type

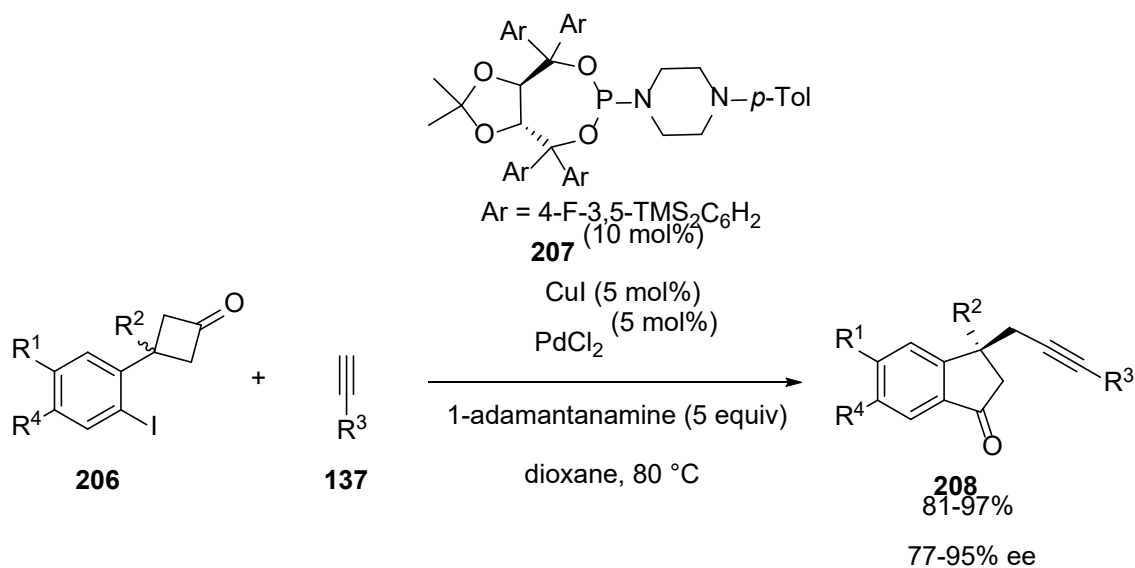
reaction was achieved between cyclohexenone **197**, Grignard reagent **200** and *N*-tosylimine **204** to afford the corresponding chiral β -aminocarbonyl compounds **205** in variable yields (20-57%), good to excellent enantioselectivities (60-99% ee) albeit combined with low diastereoselectivities (6-46% de). The first step of the sequence involved at -60 °C 5 mol% of CuBr(SMe₂) as precatalyst and 6 mol% of phosphite ligand **191** in MTBE as solvent. The second step was performed in 2-Me-THF as solvent (Scheme 71).



Scheme 71. Tandem Michael/Mannich-type reaction of cyclohexenone, Grignard reagents and a *N*-tosylimine [90].

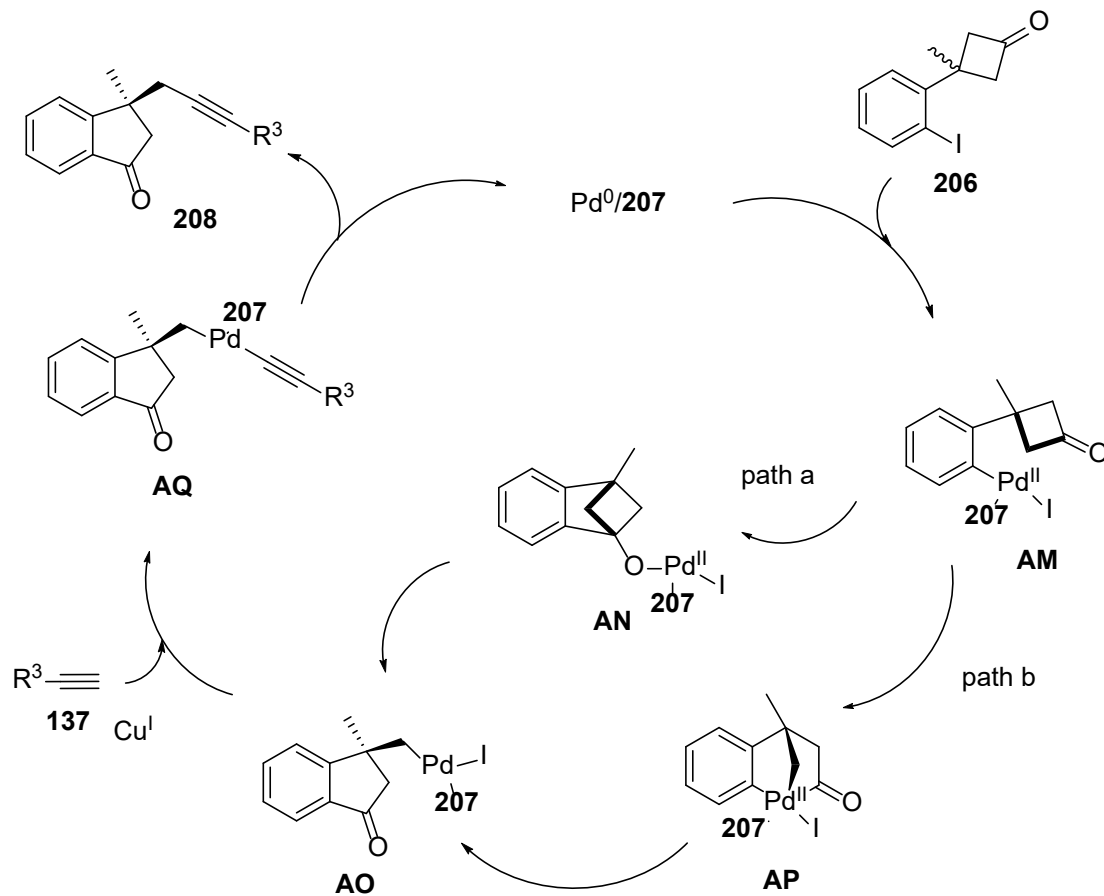
In 2019, Xu and Cao reported a novel enantioselective palladium/copper-catalyzed alkynylation of cyclobutanones **206** with terminal alkynes **137** evolving through domino C–C bond activation/Sonogashira-type cross coupling reaction (Scheme 72) [91]. To promote this one-pot reaction, the authors designed a novel chiral TADDOL-derived phosphoramidite

ligand **207** bearing fluorine and silicon-based bulky groups which was found to be an efficient promotor for both C(sp²)-C(sp³) bond cleavage and novel C(sp³)-C(sp) bond formation. The process was achieved at 80 °C by using a combination of 10 mol% of this ligand, 5 mol% of PdCl₂ and 5 mol% of CuI in dioxane as the solvent. Under these conditions, the multicatalysis allowed a range of chiral alkynylated indanones **208** bearing an all-carbon quaternary stereocenter to be synthesized from the corresponding cyclobutanones **206** and terminal alkynes **137** with both uniformly high yields (81-97%) and enantioselectivities (77-95% ee). To explain these results, the authors proposed two plausible pathways (a and b) depicted in Scheme 72. Cyclobutanone **206** underwent an oxidative addition with a Pd(0) complex to form arylpalladium species **AM**. Then, two possible pathways for the ring-opening of the cyclobutanone moiety could occur. According to pathway a, a nucleophilic addition of arylpalladium species **AM** towards the carbonyl group generated an alkoxy-palladium intermediate **AN**. A subsequent enantioselective β-carbon elimination led to σ-alkylpalladium species **AO**. According to the second pathway b, intermediate **AM** underwent a second oxidative addition with one of the C(sp²)-C(sp³) bonds of the cyclobutanone to form Pd(IV) intermediate **AP**. Then, a C(sp²)-C(sp²) reductive elimination afforded intermediate **AO**. Subsequently, σ-alkylpalladium species **AO** was trapped by terminal alkynes with the help of the CuI catalyst to form intermediate **AQ**, which gave the final 1-indanone **207** through a reductive elimination. It must be noted that this result could also appear in the first section of the review dealing with palladium-catalyzed reactions.



$R^1 = \text{H, Cl, F, Br, OMe}$
 $R^2 = \text{Me, Et, } n\text{-Bu, BnCH}_2$
 $R^3 = p\text{-MeOC}_6\text{H}_4, \text{Ph, } p\text{-(}t\text{-Bu)C}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, o\text{-FC}_6\text{H}_4,$
 $o\text{-ClC}_6\text{H}_4, m\text{-Tol, 2-thienyl, (}E\text{)-PhCH=CH, PhOCH}_2$
 $R^4 = \text{H, Me, OMe}$

proposed mechanism (with $R^1 = R_4 = \text{H, } R_2 = \text{Me}$):



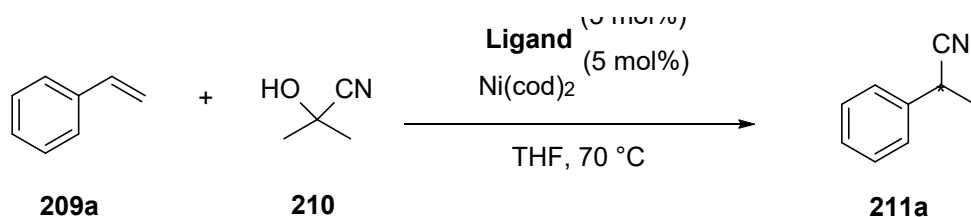
Scheme 72. Domino C–C bond activation/Sonogashira reaction of cyclobutanones with terminal alkynes [91].

6. Enantioselective nickel-catalyzed reactions

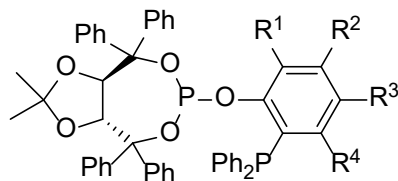
6.1. Hydrocyanations

By the very fact of the lower costs of nickel catalysts in comparison with other transition metals, a wide range of enantioselective nickel-catalyzed transformations have been developed [92]. Among them, are hydrocyanations of alkenes which play an important role in synthesis [93]. In this context, Schmalz et al. reported in 2013 the use of chiral TADDOL-derived phosphite ligands combined with Ni(cod)₂ to catalyze the asymmetric hydrocyanation of styrene **209a** with acetone cyanohydrin **210** as the cyanide source (Scheme 73) [94]. In a first time, a series of eight phosphite ligands **L1-L8** were investigated in combination with Ni(cod)₂ to promote at 70 °C and 5 mol% of catalyst loading in THF as solvent the asymmetric hydrocyanation of styrene **209a** with acetone cyanohydrin as an in situ generated source of HCN (Scheme 73). Surprisingly, the corresponding chiral branched product **211a** was obtained regioselectively with uniformly moderate to good enantioselectivities (56-68% ee) in all cases of ligands, demonstrating that the substitution pattern of the ligand backbone had only little impact on the ligand performance. In order to improve the enantioselectivity of the reaction, eight additional phosphite ligands **L9-L15** and **179** were synthesized focussing on the variation of the aryl substituents (Ar) on the TADDOL unit, since the backbone substituent(s) had little impact on the enantioselectivity. When investigated in the asymmetric hydrocyanation of styrene in optimized solvent such as methanol and at room temperature, these ligands revealed that the structural modification of the TADDOL unit indeed led to

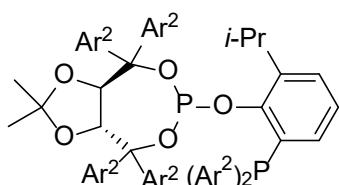
dramatic changes in the outcome of the reaction. For example, ligands **L11** and **179** provided high enantioselectivities (81-82% ee) with the non-fluorinated ligand **179** being much more active (100% yield vs 8%). Obviously, the steric hindrance of an additional substituent in the *meta*-position of the TADDOL aryl units was important for the superior performance of ligands **L11** and **179**. Again, variation of the backbone substituent R¹ (ligands **L13-L15**) had little impact on the enantioselectivities; since only ligand **L15** with a bulky *tert*-butyl group in this position was significantly less selective and active. Consequently, optimal ligand **179** (100% conversion and 81% ee) was selected for the further optimization of the reaction and its extension.



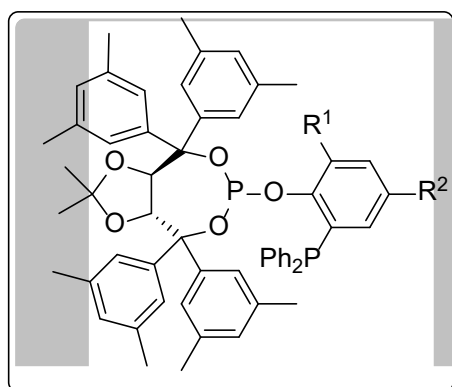
with ligands:



- L1:** R¹ = R³ = *t*-Bu, R² = R⁴ = H: 65% ee
- L2:** R¹ = *i*-Pr, R² = R³ = R⁴ = H: 68% ee
- L3:** R¹ = Ph, R² = R³ = R⁴ = H: 67% ee
- L4:** R¹ = Me, R² = R³ = R⁴ = H: 63% ee
- L5:** R¹ = *i*-Pr, R² = R³ = H, R⁴ = Me: 56% ee
- L6:** R¹ = *t*-Bu, R² = R³ = R⁴ = H: 64% ee
- L7:** R¹ = R⁴ = Me, R² = R³ = H: 56% ee
- L8:** R¹ = R² = Me, R³ = R⁴ = H: 65% ee



- L9:** Ar¹ = *p*-MeOC₆H₄, Ar² = Ph: 22%, 64% ee
- L10:** Ar¹ = Ph, Ar² = 2-Naph: 43%, 69% ee
- L11:** Ar¹ = Ph, Ar² = 3,5-(F₃C)₂C₆H₃: 8%, 82% ee
- L12:** Ar¹ = Ph, Ar₆F₅: 0%

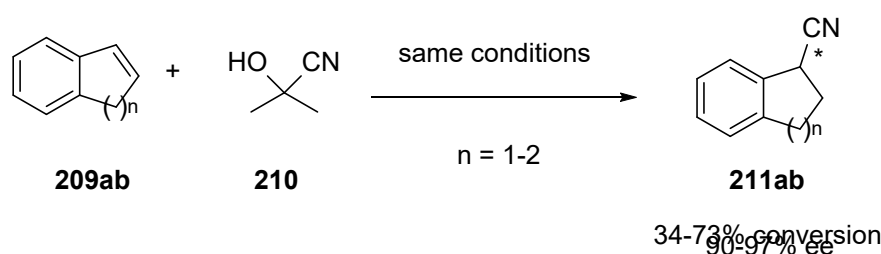
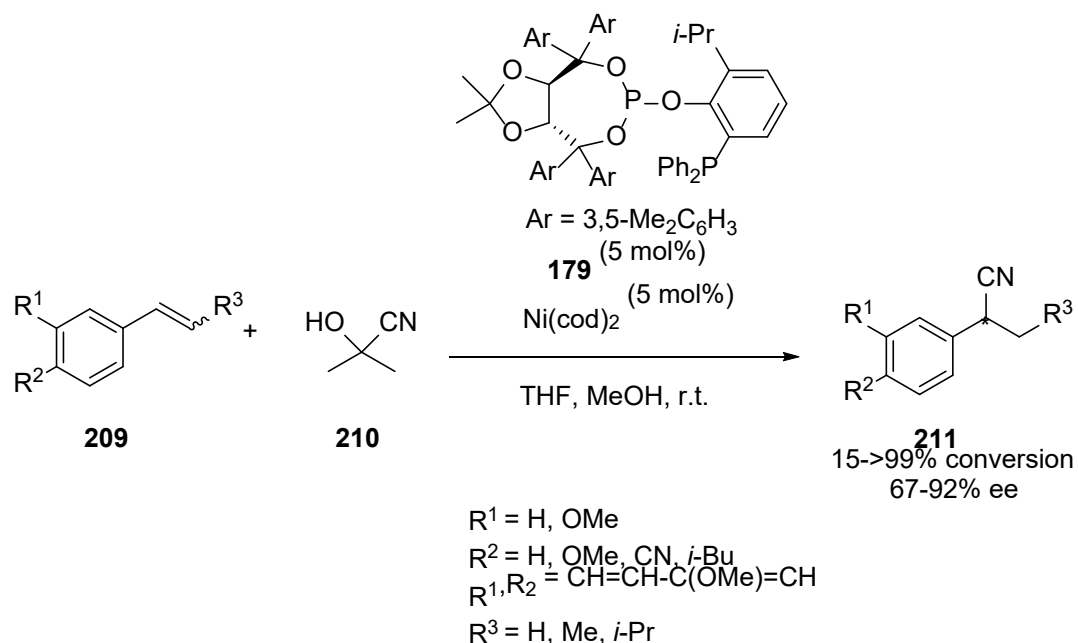


- 179:** R¹ = *i*-Pr, R² = H: 100%, 81% ee
- L13:** R¹ = Et, R² = H: 73%, 81% ee
- L14:** R¹ = Ph, R² = H: 86%, 81% ee
- L15:** R¹ = R² = *t*-Bu: 14%, 74% ee

Scheme 73. Investigation of ligands in hydrocyanation of styrene [94].

As illustrated in Scheme 74, under the optimized reaction conditions in the presence of ligand **179**, various substituted arylalkenes **209** led regioselectively to the corresponding chiral nitriles **211** with variable conversions (15-100%) and in almost all cases high

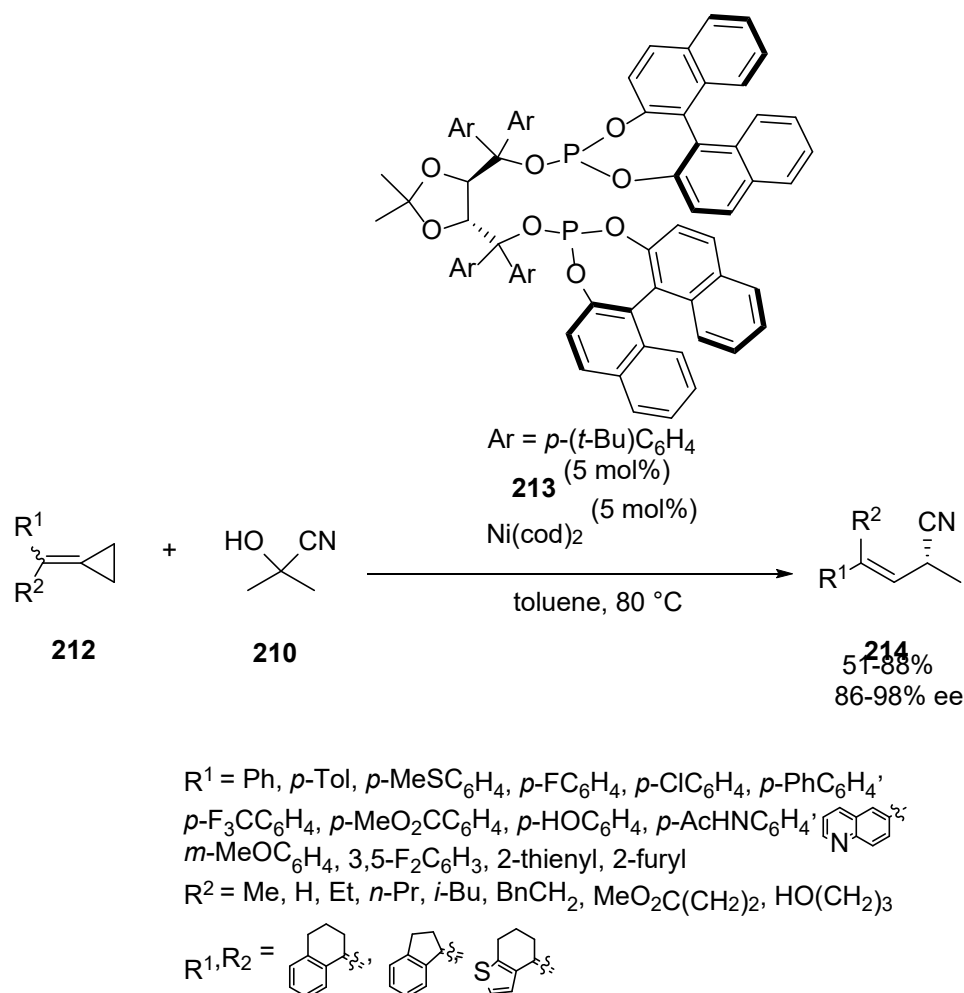
enantioselectivities (67-97% ee). The utility of this methodology was demonstrated in a synthesis of the anti-inflammatory agent ibuprofen.



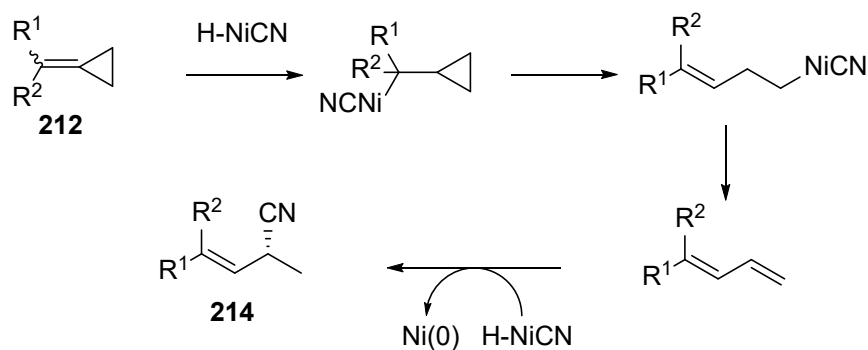
Scheme 74. Hydrocyanations of vinylarenes [94].

In 2020, Fang and Yu reported the synthesis of novel TADDOL-based diphosphite ligands which were further investigated in the enantioselective nickel-catalyzed hydrocyanation of disubstituted methylenecyclopropanes **212** with acetone cyanohydrin **210** as the cyanide source [95]. For example, by using a combination of 5 mol% of optimal chiral diphosphite ligand **213** with the same quantity of $\text{Ni}(\text{cod})_2$ as precatalyst in toluene at 80 °C, the hydrocyanation of a wide range of disubstituted methylenecyclopropanes **212** afforded the corresponding chiral allylic nitriles **214** in moderate to high yields (51-88%) and uniformly

high enantioselectivities (86-98% ee), as illustrated in Scheme 68. Actually, the process can be considered as a domino reaction since it evolves through a cyclopropane cleavage followed by a conjugated diene hydrocyanation (Scheme 75).

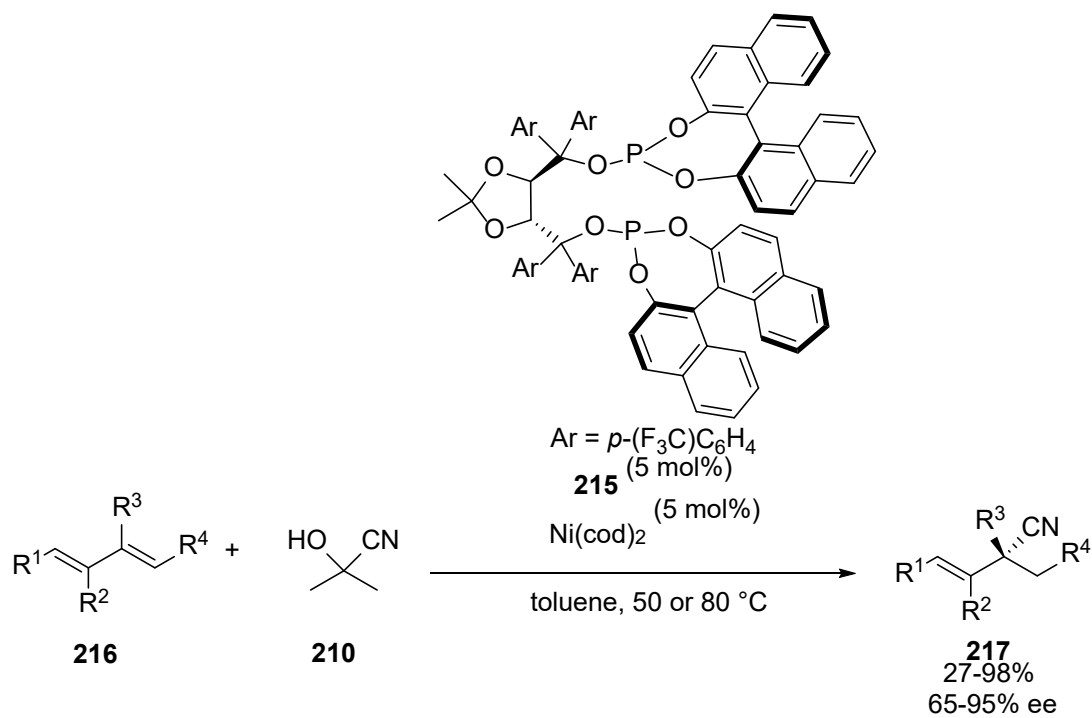


possible mechanism:

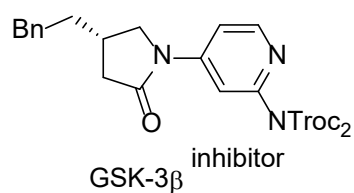


Scheme 75. Hydrocyanation of disubstituted methylenecyclopropanes [95].

The same authors employed closely related chiral TADDOL-based diphosphite ligand **215** to promote the asymmetric nickel-catalyzed 1,2-hydrocyanation of 1,3-dienes **216** with acetone cyanohydrin **210** [96]. This reaction was performed with unprecedented high levels of chemo-, enantio- and regioselectivities (Scheme 76) for either aryl-substituted 1,3-dienes or more challenging and less reactive aliphatic 1,3-dienes. It employed a combination of 5 mol% of chiral ligand **215** and the same quantity of Ni(cod)₂ as catalyst system in toluene at 50 or 80 °C. In the case of (hetero)aryl-substituted 1,3-dienes, the corresponding chiral allylic nitriles **217** were regioselectively synthesized with low to quantitative yields (27-98%) and moderate to excellent enantioselectivities (71-95% ee) without formation of 1,4-hydrocyanation products. 1-Substituted, 2-substituted, 1,2-disubstituted, 1,3-disubstituted as well as tetrasubstituted 1,3-dienes were compatible. Moreover, the reaction of various aliphatic 1,3-dienes led to the corresponding chiral allylic nitriles **217** with both moderate to high yields (53-93%) and ee values (65-92% ee). The synthetic utility of this methodology was applied to the synthesis of different drugs, such as a GSK-3β inhibitor (Scheme 76).



$\text{R}^1 = \text{Ph}, o\text{-Tol}, p\text{-FC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-NCC}_6\text{H}_4, p\text{-HOC}_6\text{H}_4,$
 $p\text{-MeO}_2\text{CC}_6\text{H}_4, o\text{-ClC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, 1\text{-Naph}, 2\text{-furyl}, 3\text{-thienyl}, 3\text{-pyridinyl},$
 $1\text{-cyclohexenyl}, \text{Cy}, \text{Me}, i\text{-Pent}, \text{CbzN} \begin{array}{c} \diagup \\ \diagdown \end{array}, \begin{array}{c} \diagup \\ \diagdown \end{array}, \begin{array}{c} \diagup \\ \diagdown \end{array}, (p\text{-MeOC}_6\text{H}_4)\text{N} \begin{array}{c} \diagup \\ \diagdown \end{array}$
 $\text{R}^2 = \text{H}, \text{Me}$
 $\text{R}^3 = \text{H}, \text{Me}$
 $\text{R}^4 = \text{H}, \text{Me}$
 $\text{R}^1, \text{R}^2 = (\text{CH}_2)_2\text{SCH}_2$

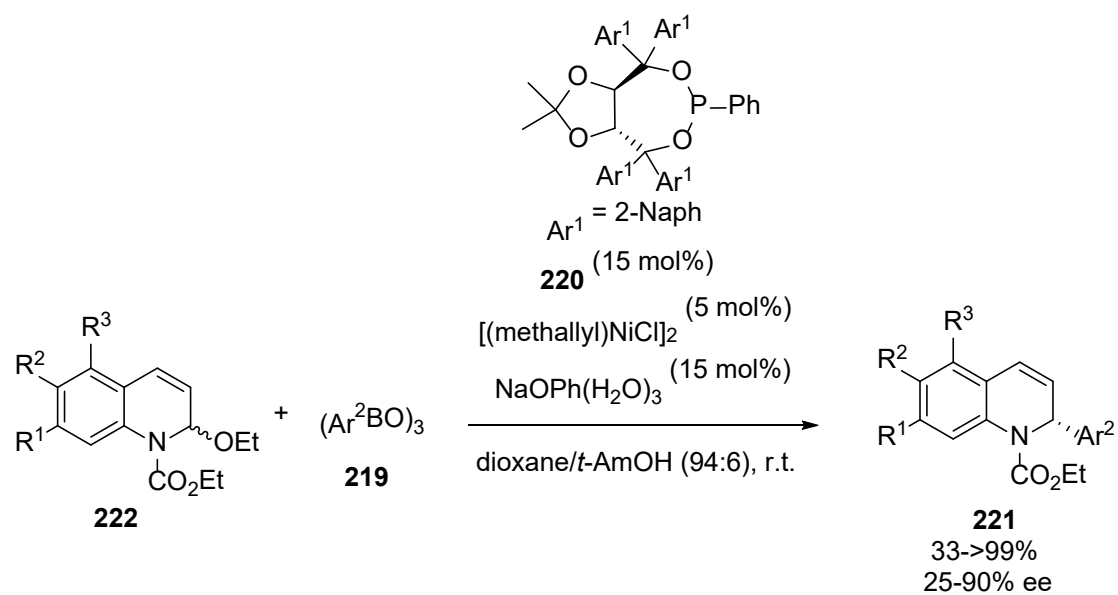


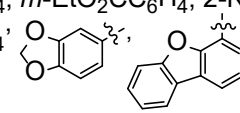
Scheme 76. Hydrocyanation of 1,3-dienes [96].

6.2. Miscellaneous reactions

In 2014, Doyle et al. reported an enantioselective nickel-catalyzed Suzuki–Miyaura cross-coupling reaction of *N,O*-acetals **222** with (hetero)arylboroxines **219** performed in the

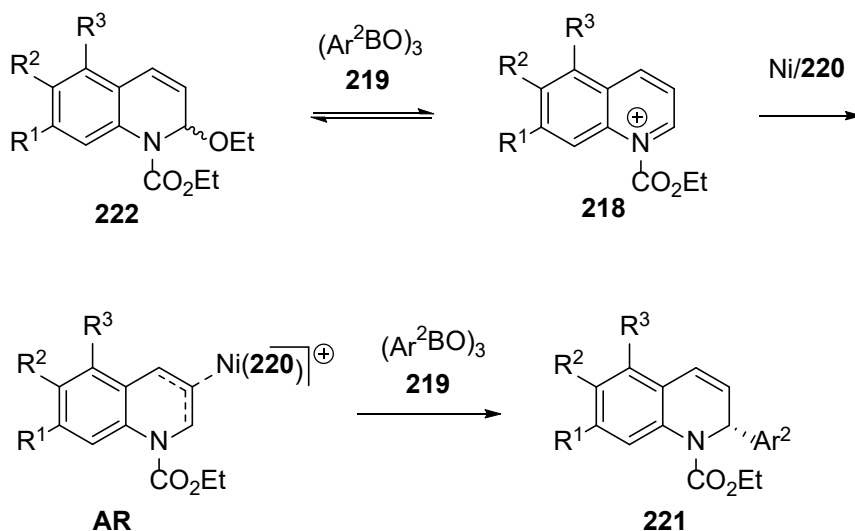
presence of a TADDOL-derived chiral monophosphorus ligand **220** to give the arylation products **221** [97]. The reaction employed a catalyst system composed of 5 mol% of [(methallyl)NiCl]₂ and 15 mol% of ligand **220** in a 96:4 mixture of dioxane and *tert*-amylic alcohol as the solvent. The quinolinium ions **218** were in situ generated from the corresponding racemic electrophiles **222** bearing an oxygen leaving group (OEt). As shown in Scheme 77, the process performed at room temperature allowed access to a series of chiral 2-(hetero)aryl-1,2-dihydroquinolines **221** which constitute important pharmaceutical scaffolds. These products were synthesized with moderate to quantitative yields (33->99%) and low to excellent ee values (25-90% ee). Substitution at the *meta*- and *para*-positions of the nucleophile was well tolerated. A variety of electron-neutral nucleophiles provided uniformly high enantioselectivities (77-87% ee) while the lowest ee value (25% ee) was observed in the reaction of an electron-deficient nucleophile ($Ar^2 = p\text{-F}_3\text{CC}_6\text{H}_4$) which also gave a moderate yield (42%). Moreover, the substitution on the quinoline ring was tolerated to a moderate extent at the 5, 6, and 7 positions. Better enantioselectivities were obtained in the reaction of substrates bearing electron-withdrawing groups on the phenyl ring while the presence of electron-donating substituents led to lower ee values. Heterocyclic boroxines were also compatible, leading to the corresponding products with high ee values (83-89% ee). As depicted in Scheme 77, the reaction evolved through the oxidative addition of Ni(0) into the quinolinium ion, in situ generated from boronate-assisted ionization of the starting material, to form key intermediate **AR** which then underwent enantioselective arylation to give the final product.



$\text{Ar}^2 = \text{Ph}, p\text{-Tol}, m\text{-Tol}, o\text{-Tol}, p\text{-FC}_6\text{H}_4, m\text{-EtO}_2\text{CC}_6\text{H}_4, 2\text{-Naph},$
 $p\text{-F}_3\text{CC}_6\text{H}_4, m\text{-MeSC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4,$


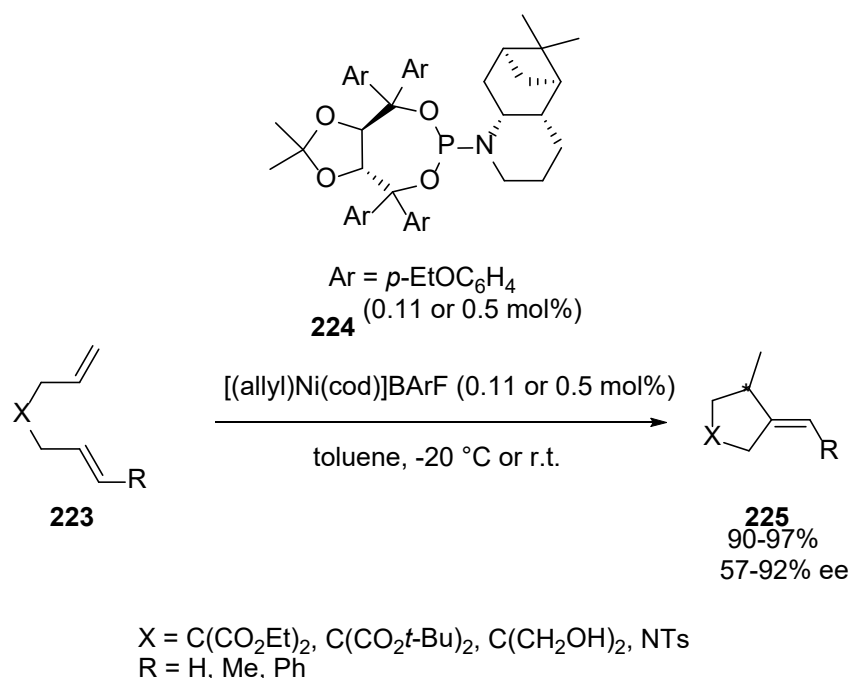
$\text{R}^1 = \text{H}, \text{Me}$
 $\text{R}^2 = \text{H}, \text{Me}, \text{CO}_2\text{Me}, \text{CF}_3, \text{OBn}$
 $\text{R}^3 = \text{H}, \text{Me}$

mechanism:



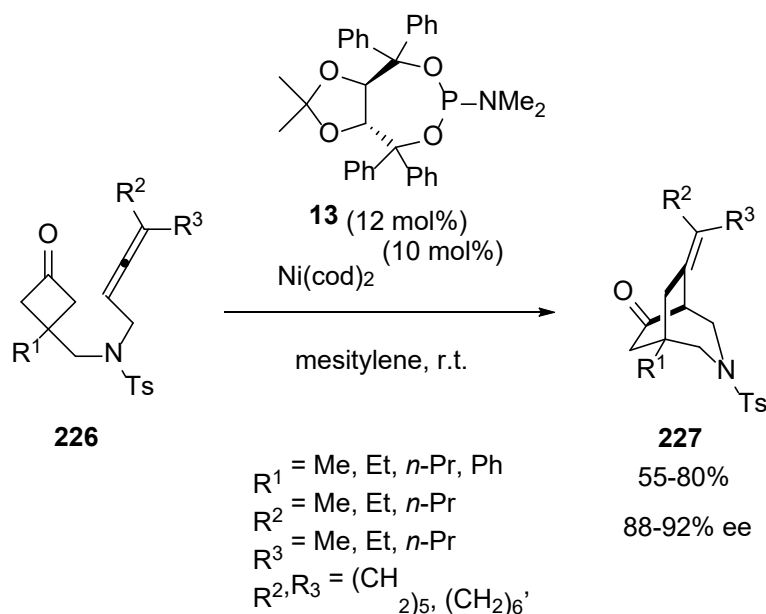
Scheme 77. Suzuki–Miyaura cross-coupling of quinolinium ions with (hetero)arylboroxines [97].

A novel library of TADDOL-based phosphoramidites was synthesized by Leitner and Francio in 2015 to be applied in the enantioselective nickel-catalyzed cycloisomerization of dienes, such as diallylic substrates **223** (Scheme 78) [98]. After selection of ligand **224** as optimal one, only 0.11 or in some cases 0.5 mol% of this ligand was combined with the same quantity of [Ni(allyl)(cod)]BARF to promote the cycloisomerization of various diallylic substrates **223** into the corresponding chiral exo-methylenecyclopentanes **225** in excellent yields (90-97%) and moderate to high enantioselectivities (57-92% ee). In addition to symmetrical dienes (R= H) which provided uniformly high ee values ($\geq 86\%$ ee), the catalyst system tolerated unsymmetrical dienes (R = Me, Ph). However, the (*E*)-diethyl allylcrotylmalonate (R = Me) underwent cycloisomerization in a less selective manner relative to symmetrical 1,6-diene substrates. The major product exo-ethylidencyclopentane with an internal *E*-configured trisubstituted double bond was formed with a regioselectivity of 56% instead of 93-99% in all other cases of substrates as well as with a lower enantioselectivity (57 % ee). Furthermore, the reaction of (*E*)-phenyl-substituted malonate substrate (R = Ph) afforded the corresponding (*E*)-exo-benzylidencyclopentane with high regio- (95%) and enantioselectivities (84% ee).

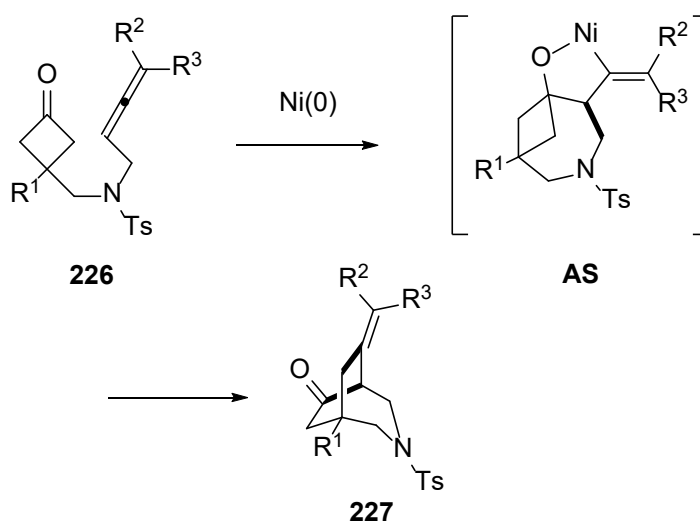


Scheme 78. Cycloisomerization of diallylic substrates [98].

Later in 2016, Dong and Zhou reported the use of a chiral nickel catalyst derived from a related chiral phosphoramidite **13** to promote an asymmetric intramolecular [4+2] cycloaddition of cyclobutanones with allenes [99]. By using 12 mol% of this ligand in combination with 10 mol% of Ni(cod)₂ as precatalyst in mesitylene as the solvent, the formal intramolecular [4+2] cycloaddition of various allenes **226** with cyclobutanones afforded the corresponding chiral [3.2.2] bicyclic products **227** as single diastereomers in moderate to good yields (55-80%) and uniformly high enantioselectivities (88-92% ee), as illustrated in Scheme 79. Dialkyl- including cycloalkyl-substituted allenes provided comparable excellent results. The authors proposed a mechanism beginning with a cyclometallation to generate a five-membered metallacycle **AS** between the carbonyl group of cyclobutanone and the unsaturated moiety of the allene. Then, this intermediate underwent a β-carbon atom elimination followed by a reductive elimination to give the final cycloadduct (Scheme 79).



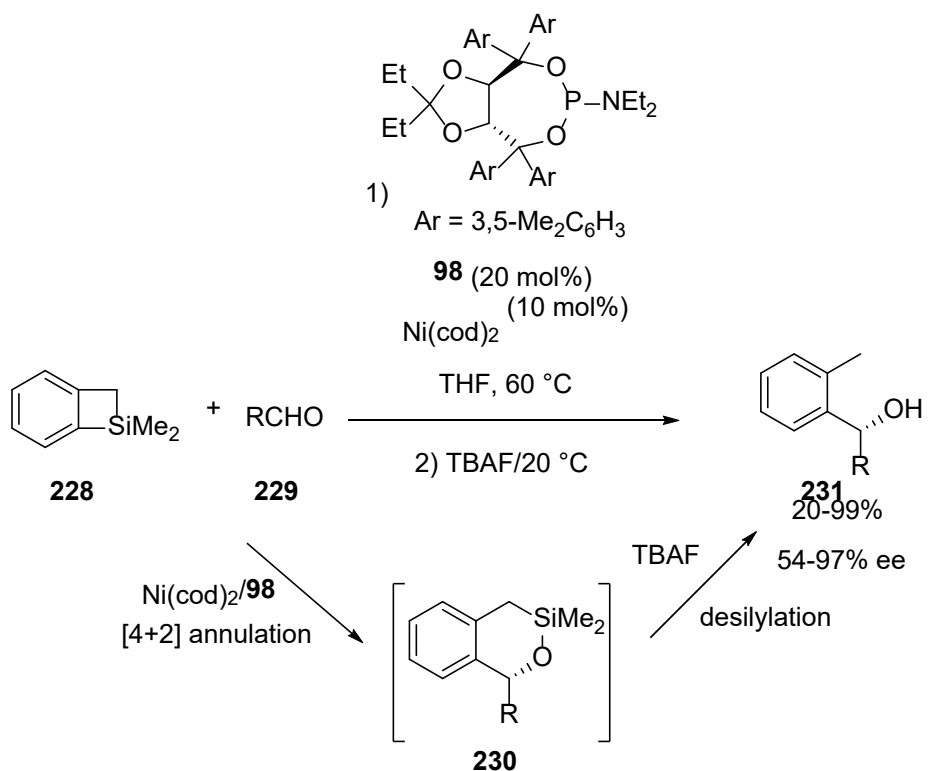
mechanism:



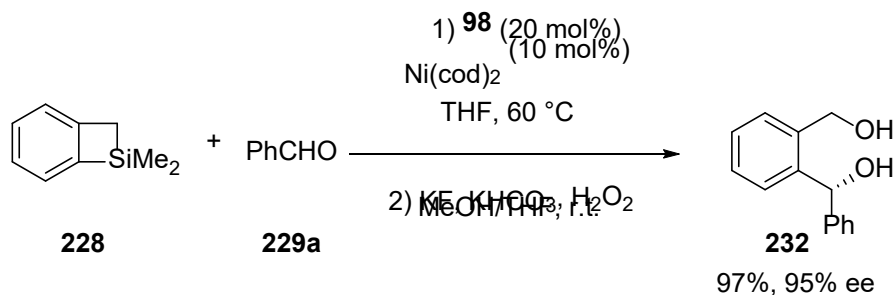
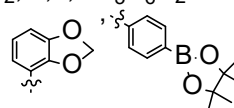
Scheme 79. Intramolecular [4+2] cycloaddition of cyclobutanones with allenes [99].

In 2022, Xu and Lan involved 20 mol% of related TADDOL-derived phosphoramidite ligand **98** in combination with 10 mol% of $\text{Ni}(\text{cod})_2$ to promote the first example of enantioselective nickel-catalyzed ring expansion of benzosilacyclobutene **228** with aldehydes **229** [100]. This [4+2] annulation occurred at 60 °C in THF as solvent to give the corresponding chiral six-membered oxasilacycles **230** which were subsequently submitted to desilylation by treatment with TBAF at room temperature to afford final *o*-tolyl arylmethanols **231** with low to quantitative yields (20-99%) and moderate to excellent enantioselectivities

(54-97% ee, as shown in Scheme 80. This tandem [4+2] annulation/desilylation reaction tolerated an impressive variety of (hetero)aromatic and even aliphatic aldehydes. Indeed, different types of substituents on the phenyl ring of aldehydes were tolerated, including electron-donating as well as electron-withdrawing groups, leading to the corresponding alcohols with both excellent yields and ee values. Functional groups, such as organoboron, ester, amide, carbamate, and olefin were all compatible, affording the desired products with 90-94% ees. The lowest yield (20%) was obtained in the reaction of a benzaldehyde exhibiting five methyl groups on the phenyl ring ($R = C_6Me_5$) albeit combined with 90% ee. Moreover, heteroaromatic aldehydes ($R = 2\text{-furyl}, 2\text{-thienyl}$) also reacted smoothly with both high yield (97%) and ee values (87-92% ee). Even aliphatic aldehydes ($R = Cy, Bn(CH_2)_2$) were tolerated but provided generally lower enantioselectivities (54-80% ee) than aromatic aldehydes. The authors demonstrated that when the desilylation step was performed in the presence of KF and H_2O_2 , the one-pot process between benzosilacyclobutene **228** and benzaldehyde **229a** resulted in the formation of chiral 1,4-diol **232** with 97% yield and 95% ee (Scheme 80). Density functional theory calculation demonstrated that the nickel catalyst activated the Si-C(sp²) bond of the benzosilacyclobutene, enabling the migratory insertion of the aldehyde into the Ni-Si bond.



R = Ph, *o*-EtC₆H₄, *o*-PhC₆H₄, *o*-FC₆H₄, *o*-MeOC₆H₄, *p*-Tol, *p*-EtC₆H₄,
p-*i*-PrC₆H₄, *p*-*t*-BuC₆H₄, *p*-PhC₆H₄, *p*-FC₆H₄, *p*-MeOC₆H₄, *p*-BnOC₆H₄,
m-PhC₆H₄, *m*-MeOC₆H₄, *m*-BnOC₆H₄, 2-Naph, *p*-MeSC₆H₄, *p*-*c*-PrC₆H₄,
p-MeO₂CC₆H₄, *p*-*t*-BuO₂CNHC₆H₄, *m*-(2-thienyl)C₆H₄, 3,5-*t*-Bu₂C₆H₃,
 3,5-MeO₂C₆H₃, 3,4-Me₂C₆H₃, 3,4-F₂C₆H₃, 3,4,5-Me₃C₆H₂, 3,4,5-F₃C₆H₂,
 2,5-MeO₂C₆H₃, Me₅C₆, *p*-(CH₂=CH)C₆H₄, Cy, Bn(CH₂)₂

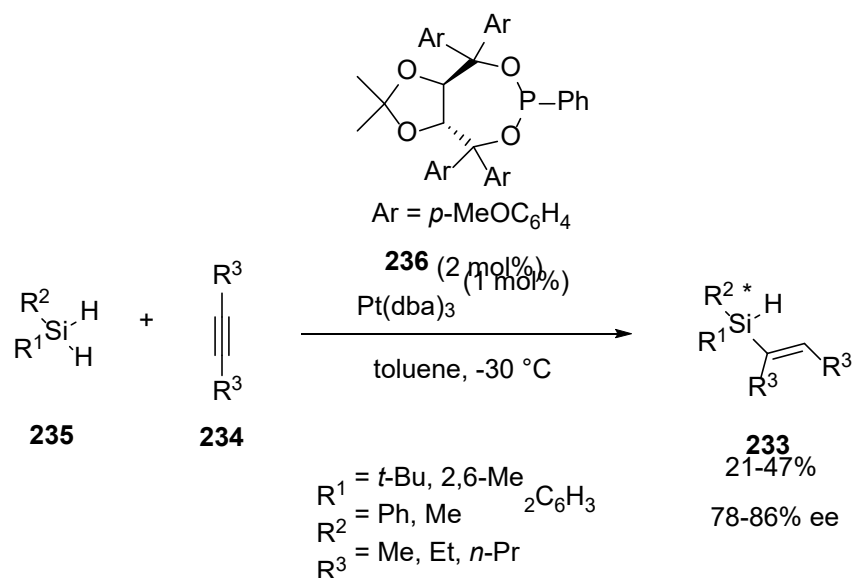


Scheme 80. Tandem [4+2] annulation/desilylation reactions of benzosilacyclobutene with aldehydes [100].

7. Enantioselective platinum-catalyzed reactions

7.1. Hydrosilylations

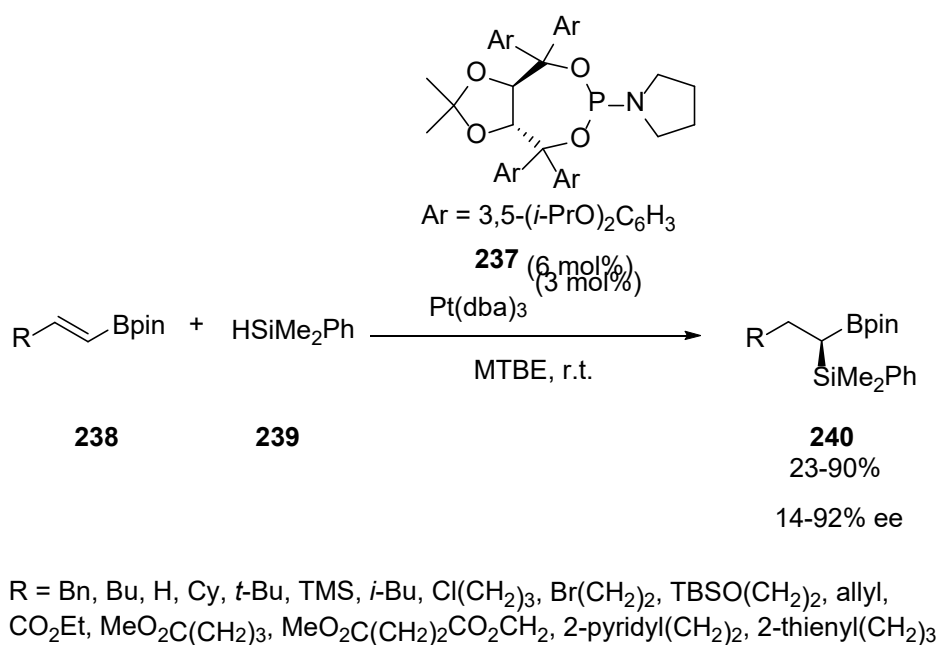
Chiral silanes possessing a silicon stereocenter have structural similarity to their carbon congeners, but show substantial differences in their physical and electronic properties [35d,101]. Therefore, nonracemic silanes have attracted attention in the fields of synthetic material and bioorganic chemistry. Since chiral silanes are unavailable in nature, the development of asymmetric methodologies for their synthesis is challenging. In this context, Tomooka et al. reported in 2012 the asymmetric synthesis of alkenylhydrosilanes **233** based on the desymmetric hydrosilylation of alkynes **234** with dihydrosilanes **235** [102]. The process was catalyzed by a chiral platinum complex in situ generated from only 1 mol% of Pt(dba)₃ and 2 mol% of chiral phosphonite ligand **236** in toluene at -30 °C. It afforded the desired chiral alkenylhydrosilanes **233** with low to moderate yields (21-47%) and uniformly high enantioselectivities (78-86% ee), as shown in Scheme 81.



Scheme 81. Hydrosilylation of alkynes with dihydrosilanes [102].

Later in 2018, Morken et al. involved chiral TADDOL-derived phosphoramidite ligand **237** in combination with the same precatalyst Pt(dba)₃ at respectively 6 and 3 mol% of catalyst loadings to promote the enantioselective hydrosilylation of alkenyl boronates **238** with

dimethylphenylsilane **239** (Scheme 82) [103]. Carried out at room temperature in MTBE as the solvent, the reaction resulted in the regioselective formation of the corresponding chiral geminal silylboronates **240** with both low to high yields (23-90%) and enantioselectivities (14-92% ee). However, in most cases of substrates, the ee values were found high ($\geq 86\%$ ee) while lower enantioselectivities (14-60% ee) were obtained in the reaction of β -branched substituents ($R = t\text{-Bu}$, Cy, TMS).

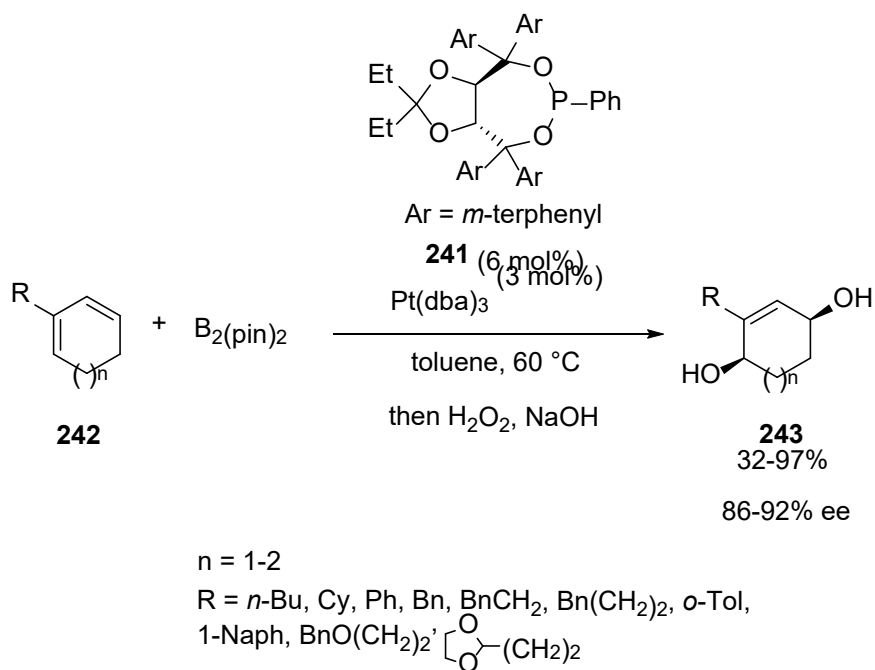


Scheme 82. Hydro-silylation of alkenylboronates with dimethylphenylsilane [103].

7.2. Diborations

The asymmetric 1,4-diboration of 1,3-dienes is a reaction that provides 2-alkene-1,4-diols after oxidative workup. In 2011, Morken and Hong reported a highly enantioselective version of this reaction by using chiral TADDOL-derived phosphonite ligand **241** (Scheme 83) [104]. This process concerned more particularly the diboration of a range of both 2-alkyl and 2-aryl-1,3-cyclohexadienes **242** with B₂(pin)₂ performed at 60 °C in toluene in the presence of 6 mol% of this ligand and 3 mol% of Pt(dba)₃ as precatalyst. After a subsequent oxidative workup with H₂O₂ and NaOH, it led to the corresponding chiral 1,4-diols **243** in both high

yields (72-97%) and enantioselectivities (86-92% ee). Even a seven-membered 1,3-diene ($n = 2$, $R = \text{Bu}$) was tolerated, giving the corresponding 1,6-diol in 92% ee albeit combined with a low yield (32%).

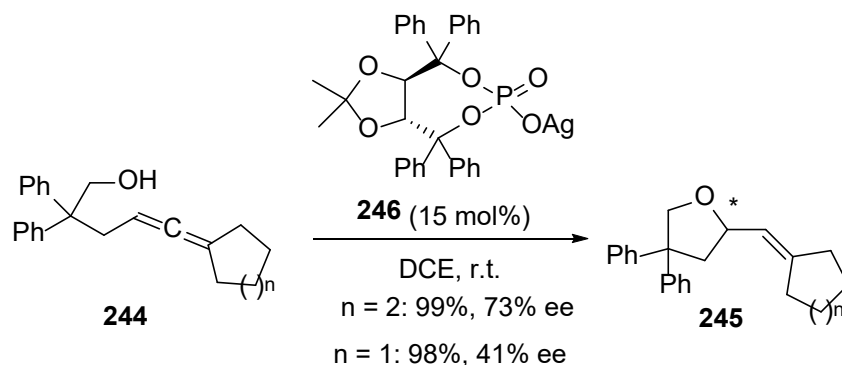


Scheme 83. 1,4-Diboration of cyclic 1,3-dienes [104].

8. Enantioselective reactions catalyzed by other metals

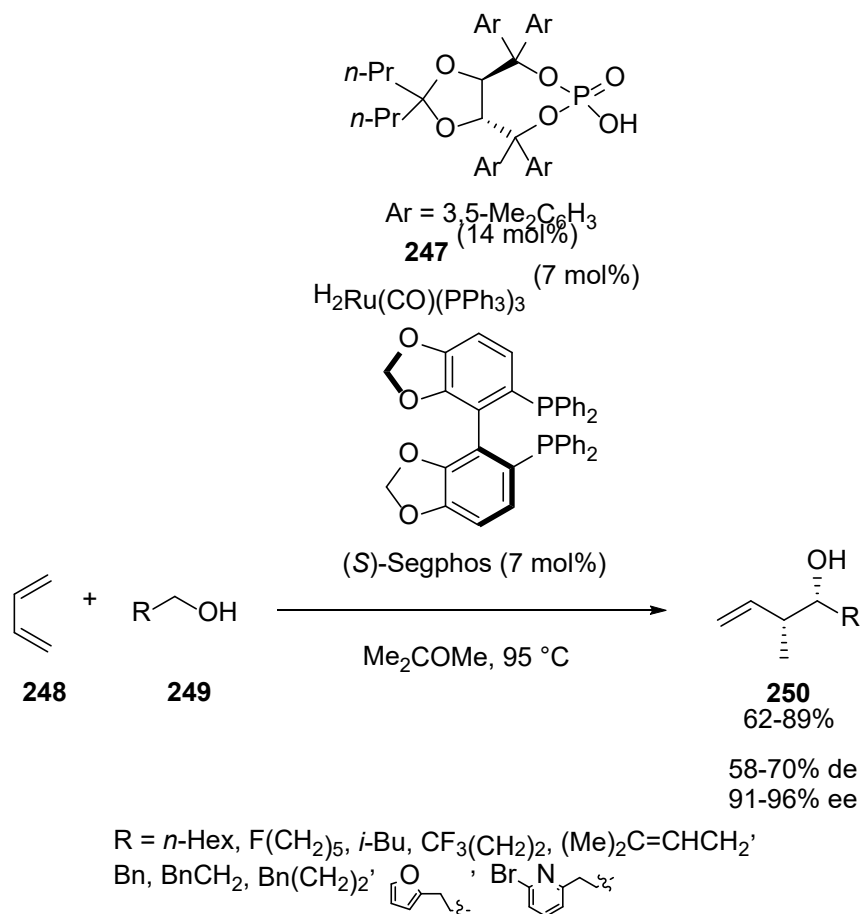
The intramolecular transition-metal-catalyzed nucleophilic addition to allenols and amino allenes constitutes a direct route to various heterocycles. While several metals are capable of promoting these reactions, silver remains one of the most effective catalysts. In 2009, Hii et al. demonstrated that intramolecular silver-catalyzed reactions of δ -allenols led regioselectively to the corresponding vinyl-substituted tetrahydrofurans through a 5-*exo-trig* cyclization, while the use of other Lewis acids, such as $\text{Sn}(\text{OTf})_2$ or $\text{Zn}(\text{OTf})_2$, favoured the 6-*exo-dig* cyclization to give tetrahydropyran rings [105]. In 2012, the same group developed the first asymmetric version of this reaction by using chiral silver catalysts. As shown in Scheme 84, quantitative yields (98-99%) combined with moderate enantioselectivities (41-73% ee) were obtained in the intramolecular asymmetric cyclization of γ -allenic alcohols **244**.

This reaction was carried out at room temperature in DCE as the solvent, yielding the corresponding chiral tetrahydrofurans **245** when promoted by 15 mol% of chiral preformed TADDOL-derived phosphate silver catalyst **246** [106].



Scheme 84. Silver-catalyzed intramolecular cyclization of γ -allenic alcohols [106].

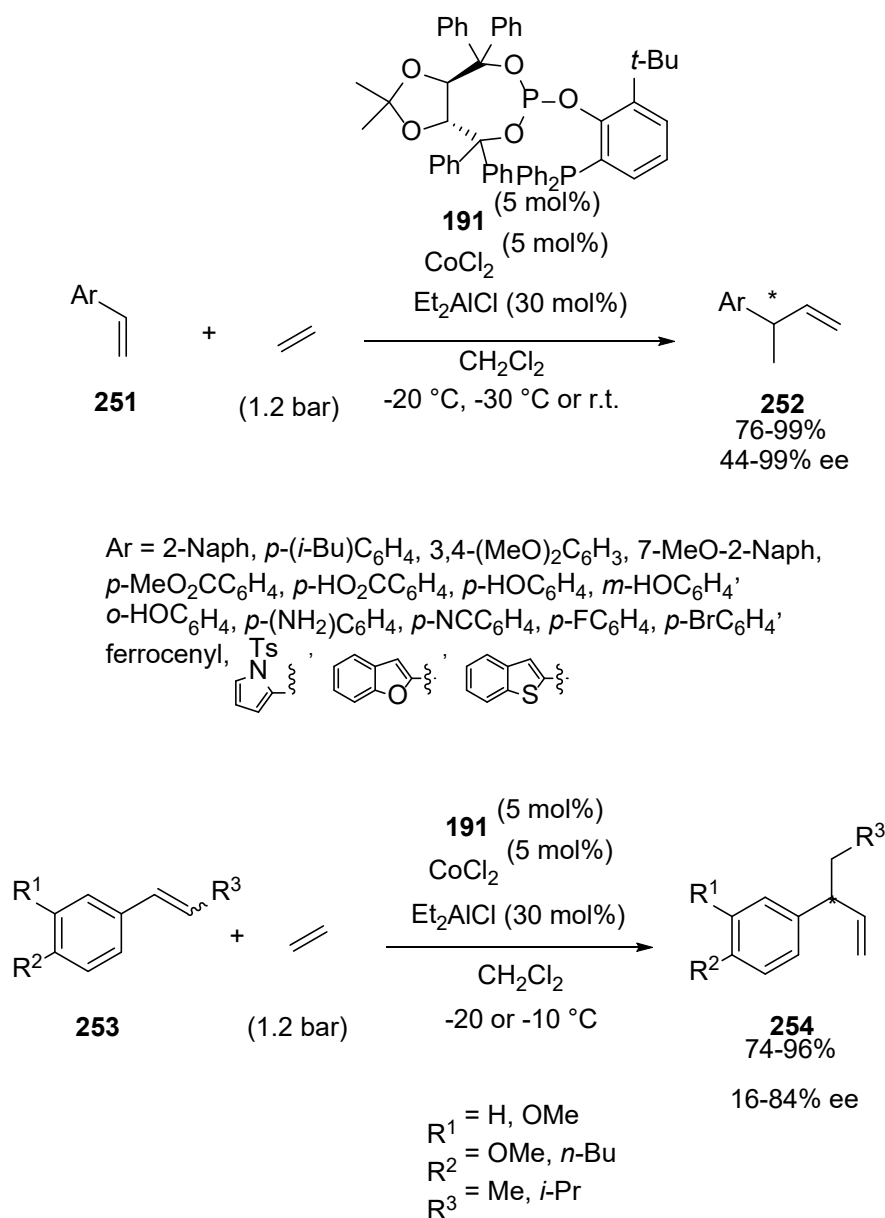
In 2012, Krische et al. disclosed that ruthenium catalysts, such as $\text{H}_2\text{Ru}(\text{CO})(\text{PPh}_3)_3$ (7 mol%), modified with (*S*)-Segphos ligand combined with chiral TADDOL-derived phosphate counterions derived from ligand **247** (14 mol%) promoted highly efficiently the diastereo- and enantioselective hydrohydroxyalkylation of butadiene **248** with primary alcohols **249** [107]. As shown in Scheme 85, this carbonyl crotylation resulted in the formation of the corresponding chiral *syn*-products **250** as major diastereomers with moderate to good diastereoselectivities (58-70% de), uniformly excellent enantioselectivities (91-96% ee) and good to high yields (62-89%). For the first time, a single-crystal X-ray diffraction data for a ruthenium complex modified by a chiral phosphate counterion was reported.



Scheme 85. Ruthenium-catalyzed hydrohydroxyalkylation of butadiene with primary alcohols [107].

In 2016, Schmalz et al. reported an efficient and practical protocol for the enantioselective cobalt-catalyzed hydrovinylation of vinylarenes **251** with ethylene at low pressure (1.2 bar) [108]. The reactions were performed in dichloromethane as solvent by using 5 mol% of a chiral cobalt catalyst in situ generated from 5 mol% of CoCl₂ the same quantity of chiral TADDOL-based phosphite ligand **191** in the presence of 30 mol% of Et₂AlCl as the activating agent. It led regioselectively to a wide range of chiral branched products **252** in high yields (76-99%) and moderate to excellent enantioselectivities (44-99% ee), as shown in Scheme 86. Moreover, related reaction conditions were applied to the asymmetric hydrovinylation of β -alkyl-styrenes **253** which regioselectively afforded the corresponding 1,4-hydrovinylation chiral products **254** in good to excellent yields (74-96%) and low to high

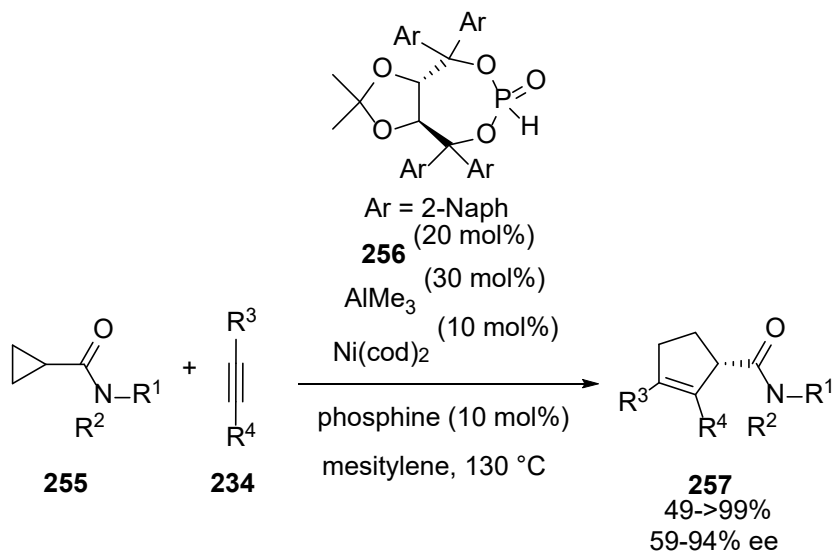
enantioselectivities (16-84% ee), as shown in Scheme 86. In both types of substrates, vinylarenes and β -alkyl-styrenes, an almost complete regioselectivity was observed ($\geq 96\%$).



Scheme 86. Cobalt-catalyzed hydrovinylation of vinylarenes and β -alkyl-styrenes [108].

In 2017, Ye et al. reported the first example of enantioselective formal [3+2] cycloaddition of unreactive cyclopropyl carboxamides **255** with alkynes **234** promoted by a chiral Ni/Al

bimetallic catalyst [109]. It employed as catalyst system, a mixture of 30 mol% of AlMe_3 , 10 mol% of $\text{Ni}(\text{cod})_2$ and 20 mol% of TADDOL-derived phosphorus ligand **256** in mesitylene as the solvent. Performed at 130 °C in the presence of 10 mol% of a tertiary phosphine ($\text{PR}_3 = \text{P}(o\text{-Tol})_3$, $\text{Cy}_2\text{P}[2,4,6\text{-}(i\text{-Pr})_3\text{C}_6\text{H}_2]$ or Cy_2PPh) as an additive, the reaction afforded a series of chiral cyclopentenyl carboxamides **257** with moderate to quantitative yields (49->99%) and moderate to excellent enantioselectivities (59-94% ee), as illustrated in Scheme 87. A range of symmetrical diarylalkynes bearing various substituents on the phenyl ring were compatible, leading to the corresponding products with good to high yields (60-99%) and homogeneously high enantioselectivities (86-94% ee). Moreover, the reaction of a diheteroaromatic alkyne ($\text{R}^3 = \text{R}^4 = 3\text{-thienyl}$) also provided a high ee value (86% ee). In contrast, both lower enantioselectivities and yields (43-63%) were obtained when using symmetrical dialkylalkynes (59% ee with $\text{R}^3 = \text{R}^4 = n\text{-Bu}$) or unsymmetrical dialkylalkynes (77% ee with $\text{R}^3 = \text{Me}$, $\text{R}^4 = \text{TMS}$). Moreover, when the pyrrolidinyl moiety of the amide ($\text{R}^1, \text{R}^2 = (\text{CH}_2)_5$) was changed into other amine groups ($\text{R}^1, \text{R}^2 = (\text{CH}_2)_2\text{O}(\text{CH}_2)_2$, or $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Ph}$), the enantioselectivities of the reaction decreased significantly (65-75% ee), albeit with quantitative yields, suggesting that the stereoselective control of the process was highly sensitive to steric hindrance of both amides and alkynes. A mechanism presented in Scheme 87 begins with the formation of intermediate **AT** from the ligand, $\text{Ni}(\text{cod})_2$ and AlMe_3 . The latter coordinates with the cyclopropyl carboxamide to form intermediate **AU**. A subsequent tertiary phosphine-assisted oxidative addition of nickel with the C–C bond of the cyclopropane leads to four-membered nickelacycle **AV**. Then, this intermediate inserts into the alkyne to afford six-membered nickelacycle **AW**. A final reductive elimination furnishes the cyclopentenyl carboxamide and regenerates the catalytic species.



phosphine = $\text{P}(\text{o-Tol})_3$, $\text{Cy}_2\text{P}[2,4,6\text{-}(i\text{-Pr})_3\text{C}_6\text{H}_2]$ or Cy_2PPh

$\text{R}^1, \text{R}^2 = (\text{CH}_2)_5, (\text{CH}_2)_2\text{O}(\text{CH}_2)_2$

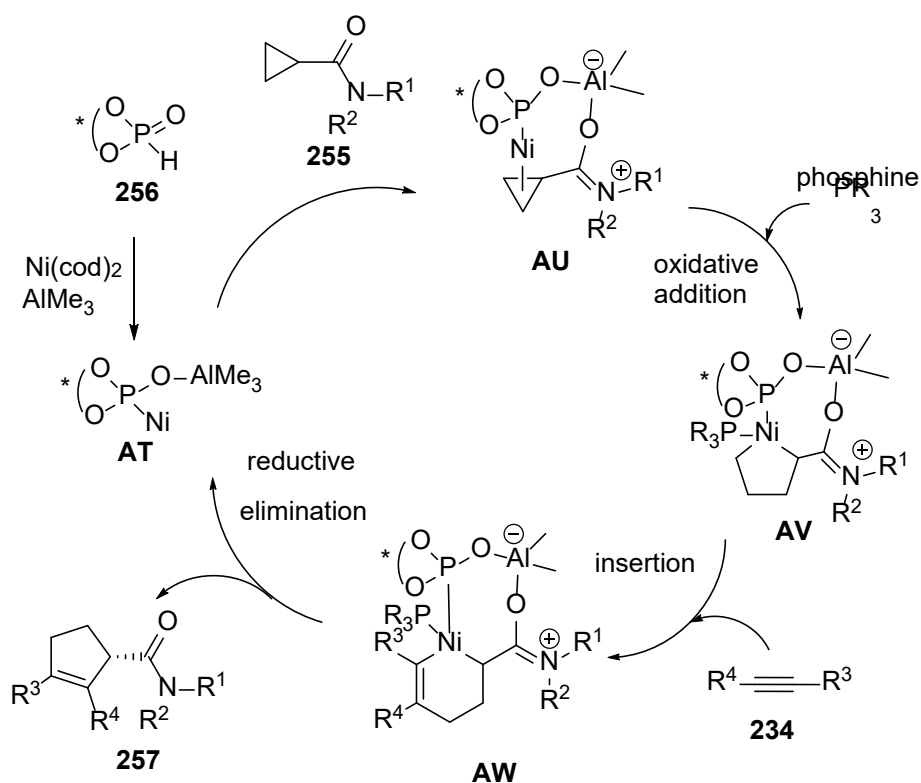
$\text{R}^1 = \text{Me}$

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

$\text{R}^3 = \text{Ph}, p\text{-Tol}, p\text{-MeOC}_6\text{H}_4, o\text{-MeOC}_6\text{H}_4, m\text{-MeOC}_6\text{H}_4, p\text{-F}_3\text{COC}_6\text{H}_4,$
 $p\text{-FC}_6\text{H}_4, 3\text{-thienyl}, o\text{-Tol}, m\text{-Tol}, p\text{-EtC}_6\text{H}_4, p\text{-}t\text{-BuC}_6\text{H}_4, n\text{-Bu}$

$\text{R}^4 = \text{Ph}, p\text{-Tol}, p\text{-MeOC}_6\text{H}_4, o\text{-MeOC}_6\text{H}_4, m\text{-MeOC}_6\text{H}_4, p\text{-F}_3\text{COC}_6\text{H}_4,$
 $p\text{-FC}_6\text{H}_4, 3\text{-thienyl}, o\text{-Tol}, m\text{-Tol}, p\text{-EtC}_6\text{H}_4, p\text{-}t\text{-BuC}_6\text{H}_4, n\text{-Bu}, \text{TMS}$

proposed mechanism:



Scheme 87. Formal [3+2] cycloaddition of cyclopropyl carboxamides with alkynes catalyzed by a Al/Ni bimetallic catalyst [109].

9. Conclusions

Since the discovery of TADDOL-based phosphorus ligands by Seebach in 1993, the application of these remarkable ligands in asymmetric metal catalysis has expanded rapidly.

This review demonstrates the high performance of these ligands to promote a wide diversity of metal-catalyzed highly enantioselective reactions. The success of these ligands is related to their straightforward and modular synthesis from an inexpensive chiral source available in both enantiomeric forms. Moreover, their scaffolds are easily modifiable at multiple sites, making them finely tunable to allow optimization of enantioselectivity and efficiency in asymmetric catalysis. Consequently, these ligands with finely adjustable steric and electronic properties have been combined with a range of metals, such as palladium, rhodium, gold, copper, nickel, platinum, cobalt, ruthenium, silver and aluminum, to catalyze many types of enantioselective transformations with high efficiencies and enantioselectivities. Among them are C–H functionalizations, such as atroposelective arylations, cross-couplings, allylic substitutions, cycloadditions, hydroborations, hydrocyanations, hydrosilylations, hydroformylations, hydrovinylation, hydrogenations, Heck reactions, Nazarov-type reactions, Michael additions, ring-opening reactions, cyclizations of many types, such as cycloisomerizations, as well as more complex processes, such as domino and tandem reactions. Especially, monophosphorus ligands, such as versatile TADDOL-derived phosphoramidites which have been the most employed in the last decade, along with analogous phosphites and phosphonites, have enabled access to a wide structurally diverse range of valuable chiral products via C–C bond formations with remarkable chemo-, regio-

and enantioselectivities. It must be noted that along with this type of widely employed monophosphorus ligands, others phosphorus ligands derived from TADDOL have been successfully applied to promote a variety of enantioselective metal-catalyzed reactions, such as phosphoric acids, biphosphines, biphosphites and diamidophosphites among others. Despite these intense developments, numerous interesting transformations are yet to be discovered. It is therefore important to continue the design and exploration of novel chiral phosphorus ligands based on TADDOL with various structural features. Such practice will undoubtedly continue in the future. An effort towards more structural and computational studies will have to be made to shed light upon the origin of the enantioselectivity of the reactions. Furthermore, more applications of these transformations in the total synthesis of important products are awaited.

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