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Coordination-assisted, transition-metal-catalyzed enantioselective desymmetric C–H functionalization

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Transition-metal-catalyzed asymmetric C–H functionalization has gradually emerged as a powerful tool for the creation of structural and chiral complexity in an atom- and step-economical fashion. The nature of this strategy provides a variety of methodologies to overcome the limitation of enantioselective desymmetrization caused by the synthesis of preformed multifunctional symmetric substrates. This review aims to summarise recent advances in transition-metal-catalyzed enantioselective desymmetric C–H functionalization reactions *via* coordination-assisted metal insertion, covering the literature from 2008 to June 2021. The mechanistic pathway and the modes of stereocontrol are discussed where appropriate.

1. Introduction

Over the past decades, the enantioselective desymmetrization strategy, as one of the versatile and powerful tools for the transformation of simple molecules to complex chiral scaffolds, has been widely used in the synthesis of natural products, bioactive molecules, and chiral ligands.[1] However, the use of preformed multifunctional symmetric substrates is necessary in various types of desymmetric reactions, which is against the nature of step-economy and largely limits the diverse functionalities of the newly formed products. Meanwhile, transition-metal-catalyzed asymmetric C–H functionalization has been an attractive approach in synthetic chemistry due to its ability to construct complex chiral molecules in a more straightforward, convenient, and efficient way.[2] Several strategies have been developed to enable the enantio-

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Zhuo-Zhuo Zhang

Zhuo-Zhuo Zhang was born in Xian, China, and received her BSc degree from Shaanxi Normal University in 2014. In 2019, she received her PhD from Zhejiang University under the supervision of Professor Bing-Feng Shi. She then began her independent career in the School of Food and Biological Engineering of Chengdu University. Her lab currently focuses on developing novel methodologies in the area of base metal catalyzed C–H activation.

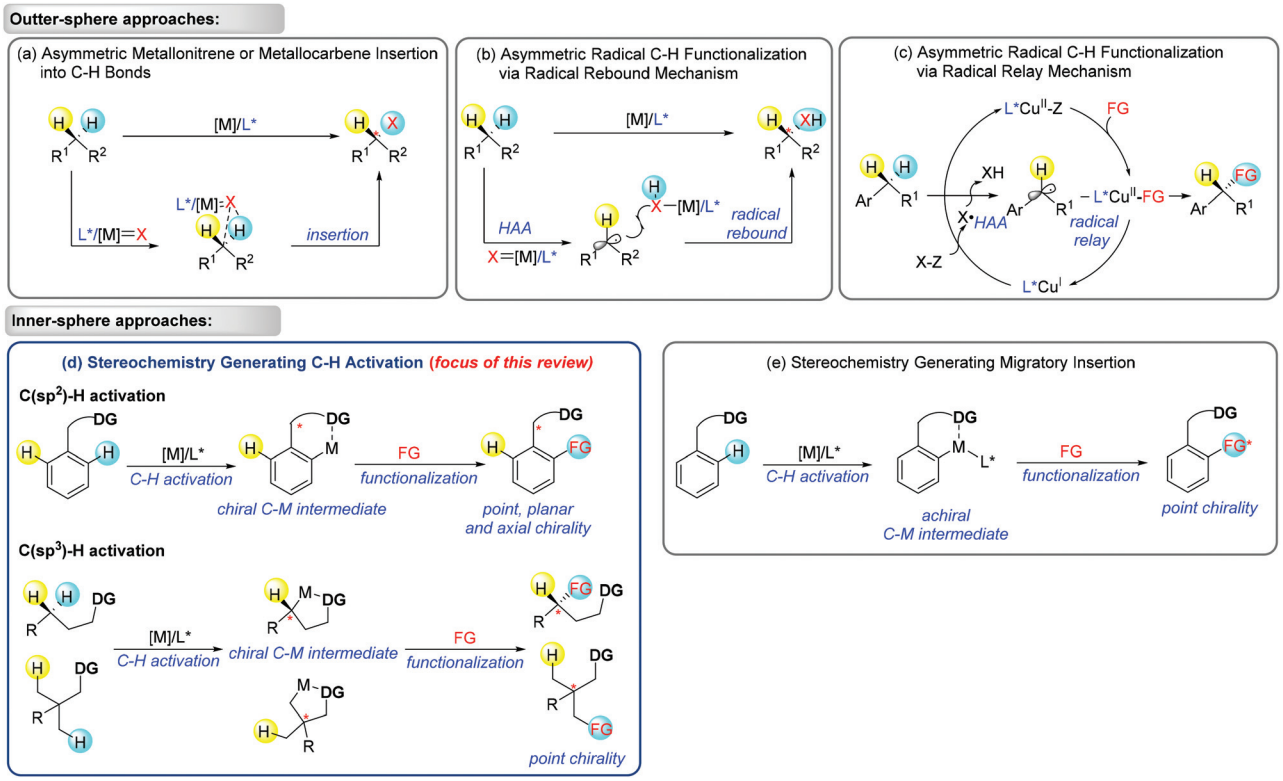


Fig. 1 General mechanisms for transition-metal-catalyzed enantioselective C–H bond functionalizations. DG = directing group.

selective desymmetrization of C–H bonds. Generally speaking, two mechanistic pathways are involved (Fig. 1): (i) an outer-sphere mechanistic pathway without the involvement of direct interaction between the C–H bond and the metal center and (ii) an inner-sphere mechanism proceeding through C–H bond cleavage to generate carbon–metal intermediates.[3] The outer-sphere mechanism commonly involves the interaction of the chiral ligand with the C–H bonds or a hydrogen atom transfer (HAT) pathway, which could be classified into the following three categories: (a) metallonitrene or metallocarbene insertions (Fig. 1a);[4] (b) radical transformations operating through hydrogen atom abstraction (HAA) followed by radical rebound (Fig. 1b);[5] and (c) radical transformations operating through hydrogen atom abstraction followed by radical relay (Fig. 1c).[6]

Jun-Long Niu

Jun-Long Niu graduated in Chemistry in 2004 from Zhengzhou University and obtained his PhD from the same institution in 2009 under the supervision of Professor Mao-Ping Song. He joined the faculty of Zhengzhou University in 2011 and is currently a professor in the College of Chemistry. His research interests lie broadly within the area of organometallic chemistry with a particular focus on inexpensive metal-catalyzed C–H functionalization.

Bing-Feng Shi

Bing-Feng Shi grew up in Shandong, China, and received his BSc degree from Nankai University in 2001 and PhD from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, under the guidance of Professor Biao Yu in 2006. Following a stint as a postdoctoral fellow at the University of California, San Diego (2006–2007), he moved to The Scripps Research Institute working with Professor Jin-Quan Yu as a research associate. In 2010, he joined the Department of Chemistry at Zhejiang University as a professor. His research focus is transition-metal-catalyzed C–H functionalization and its synthetic applications.

In contrast, in the inner-sphere strategy, the direct insertion of the transition metal into the C–H bond results in the formation of a carbon–metal intermediate which is then followed by further functionalization.[7] In this context, the introduction of chirality could take place either *via* an enantio-determining metal insertion to generate a chiral carbon–metal intermediate (Fig. 1d) or *via* a stereocontrolled migratory insertion of an unsaturated species, such as alkene, allenes, carbonyl, *etc.*, into an achiral carbon–metal intermediate (Fig. 1e). This first stereochemistry generating approach has demonstrated great potential in the creation of a wide range of optically active compounds through diverse functionalization reactions to create point, axial and planar chirality, which will be the focus of this review (Fig. 1d).

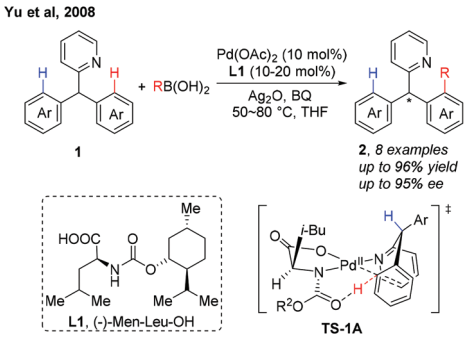
Although transition-metal-catalyzed enantioselective C–H functionalizations have been reviewed by several groups from different specific aspects,[8] a comprehensive overview based on the desymmetric strategies has not been presented yet. Hence, a timely review discussing the developments in this exciting and fast developing field is highly desired. In this review, we aim to provide a summary of coordination-assisted, enantioselective C–H functionalizations *via* a desymmetric strategy involving stereodetermination of C–H cleavage to form a chiral carbon–metal intermediate that covers the full breadth of transition metal catalysts. Advances published from 2008 to June 2021 will be discussed based on the types of C–H bonds and the corresponding transformations. The mechanistic pathway and the modes of stereocontrol are discussed where appropriate. It is to be noted that intramolecular enantioselective C–H functionalization initiated by the oxidative addition of a metal catalyst into Ar–X or Si–H bonds has been thoroughly reviewed and is not discussed here.[9]

2. Desymmetric C(sp^2)–H functionalization

In the last few years, transition-metal-catalyzed asymmetric C(sp^2)–H functionalization has been well developed as an efficient approach for the construction of point, axial and planar chirality by desymmetrization of *gem*-diaryl and biaryl compounds as well as ferrocene derivatives. In this part, we discuss the developments on the basis of the type of functionalization, such as alkylation, arylation, alkenylation, annulation, and C–heteroatom formation.

2.1 Alkylation

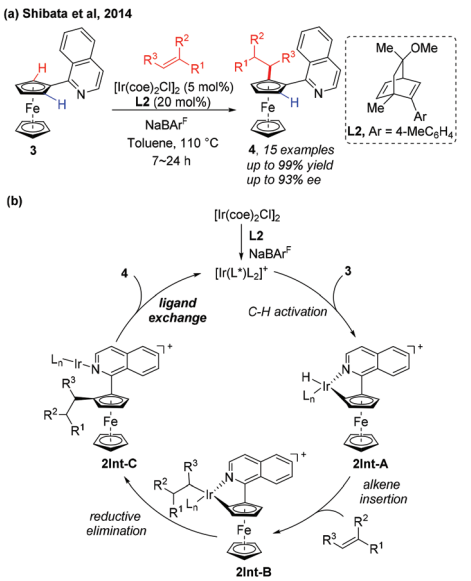
In 2008, Yu and coworkers made a significant breakthrough in Pd(II)-catalyzed enantioselective C(sp^2)–H activation reaction by the use of mono-*N*-protected amino acids (MPAAs) as chiral ligands (Scheme 1).[10] In the use of (−)-Men-Leu-OH **L1** as the ligand enables asymmetric C–H alkylation of diphenyl(2-pyridyl)methane **1** with alkyl boronic acids, providing the desired products **2** in excellent yields and enantioselectivities (up to 96% yield and 95% ee). The reaction proceeds through a Pd(II)/Pd(0) catalytic cycle involving an



Scheme 1 Pd(II)-Catalyzed enantioselective C(sp^2)–H alkylation.

enantio-determining step. Since this pioneering work, MPAA ligands have been widely applied in Pd(II)-catalyzed enantioselective C–H functionalization.[8j] Experimental and computational studies of the related Pd(II)/MPAA catalysis suggest that the MPAA ligand acts as a dianionic *N*,*O*-bidentate ligand and the amidate group participates as an internal base in the concerted-metalation–deprotonation (CMD) process.[8i,11] The enantio-determining C–H cleavage step has been proposed to occur through a transition state to minimize the steric repulsion between the substrate and the side chain of the MPAA ligand (**TS-1A**).

In 2014, Shibata and Shizuno disclosed an Ir(I)-catalyzed enantioselective C–H alkylation of (isoquinolin-1-yl)ferrocenes **3** with various alkenes using the chiral diene ligand **L2** (Scheme 2a).[12] An array of alkenes, such as allylsilane, oct-1-ene, styrene, and norbornene, was well tolerated, affording the corresponding alkylated ferrocene derivatives **4** in good to high yields with good enantioselectivities. Notably, directing group screening shows that the use of isoquinolyl moiety



Scheme 2 Ir(I)-Catalyzed enantioselective intermolecular C(sp^2)–H alkylation of ferrocenes.

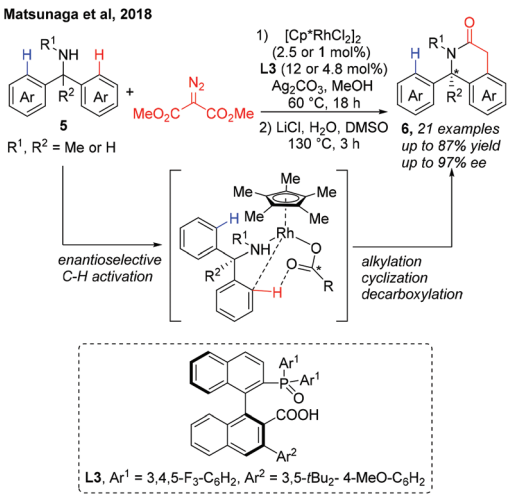
allows the formation of mono-substituted ferrocene derivatives with excellent regioselectivity as well as high enantioselectivity. A plausible Ir(I)/Ir(III) catalytic cycle is proposed in Scheme 2b. First, a cationic $[Ir(L^*)L_2]^+$ species was generated upon treatment of the $[Ir(coe)_2Cl]_2$ catalyst with chiral diene ligands and $NaBAr^F$, which underwent the oxidative C–H bond cleavage, to afford the five-member intermediate **2Int-A**. Migratory insertion of the alkene into the Ir–H bond of **2Int-A** would occur in linear or branched fashion, leading to intermediates **2Int-B**. Reductive elimination of **2Int-B** gave the major linear isomer of the alkylated ferrocene **4** with the regeneration of the Ir(I) complex.

Later in 2018, Lin, Yoshino, Matsunaga and coworkers employed an achiral $Cp^xRh(III)$/chiral carboxylic acid (CCA) catalytic system[13] to accomplish the desymmetric C–H alkylation of diarylmethanamines with diazomalonates.[14] The subsequent cyclization and decarboxylation led to the potentially bioactive 1,4-dihydroisoquinolin-3(2*H*)-ones **6** (Scheme 3). Unlike the former studies in which a chiral Cp^x ligand was generally necessary in the stereocontrol C–H cleavage step,[15] the enantioselective C–H activation in this catalysis could be achieved *via* a carboxylate-assisted enantio-determining CMD-type C–H cleavage using a novel binaphthyl based chiral monocarboxylic acid **L3** as the only source of chirality.

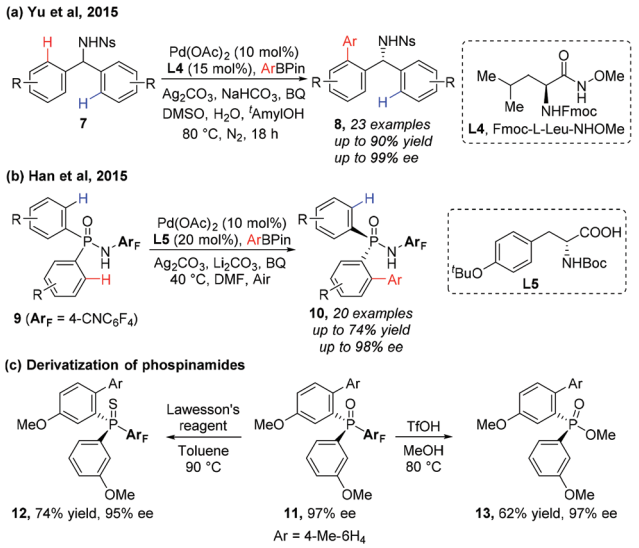
2.2 Arylation

Encouraged by their initial success in Pd-catalyzed asymmetric alkylation using the MPAA ligands,[10] the Yu group further examined the enantioselective arylation of C(sp^2)–H bonds *via* a similar Pd(II)/Pd(0) catalytic cycle in 2015. They successfully achieved the Pd(II)-catalyzed enantioselective C–H arylation of diarylmethylamines **7** with organoborons using *N*-methoxyamides **L4** as the chiral ligand (Scheme 4a).[16a] Notably, the *para*-nitrobenzenesulfonamide directing group could be easily removed under mild conditions.

In the same year, a Pd(II)-catalyzed desymmetric C(sp^2)–H arylation of diarylphosphinamides **9** with boronic esters using



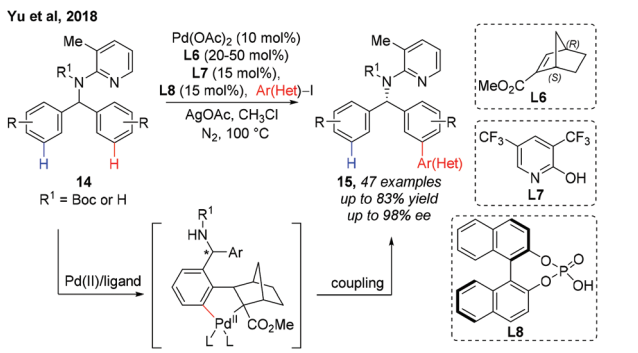
Scheme 3 $Cp^xRh(III)$/chiral acid-catalyzed enantioselective intermolecular C(sp^2)–H alkylation of diarylmethamines.



Scheme 4 Pd(II)-Catalyzed enantioselective C(sp^2)–H arylation and derivatization.

Boc-*N*-protected amino acids **L5** as the chiral ligand was reported by the Han group (Scheme 4b).[16b] The arylated chiral diarylphosphinamides **11** could be easily converted into potentially useful *P*-stereogenic derivatives, such as chiral thiophosphinamide **12** and methyl phosphinate **13**, with a negligible decrease in enantiomeric excess (Scheme 4c).

Although several Pd-catalyzed enantioselective *ortho*-C(sp^2)–H functionalization reactions have been developed, the enantioselectivity in remote C(sp^2)–H activation remains a significant challenge because the metal insertion is too far away from the resulting stereogenic carbon centre. In 2018, the Yu group designed a novel chiral transient mediator to realize an unprecedented Pd(II)-catalyzed enantioselective *meta*-C(sp^2)–H arylation and alkylation (Scheme 5).[17] Mechanistically, the chirality inducing step proceeds *via* the insertion of enantio-enriched norbornene **L6** to the *ortho* palladate intermediate. In the presence of the chiral transient mediator (+)-NBE-CO_2Me **L6**, a broad range of substituted aryl iodides

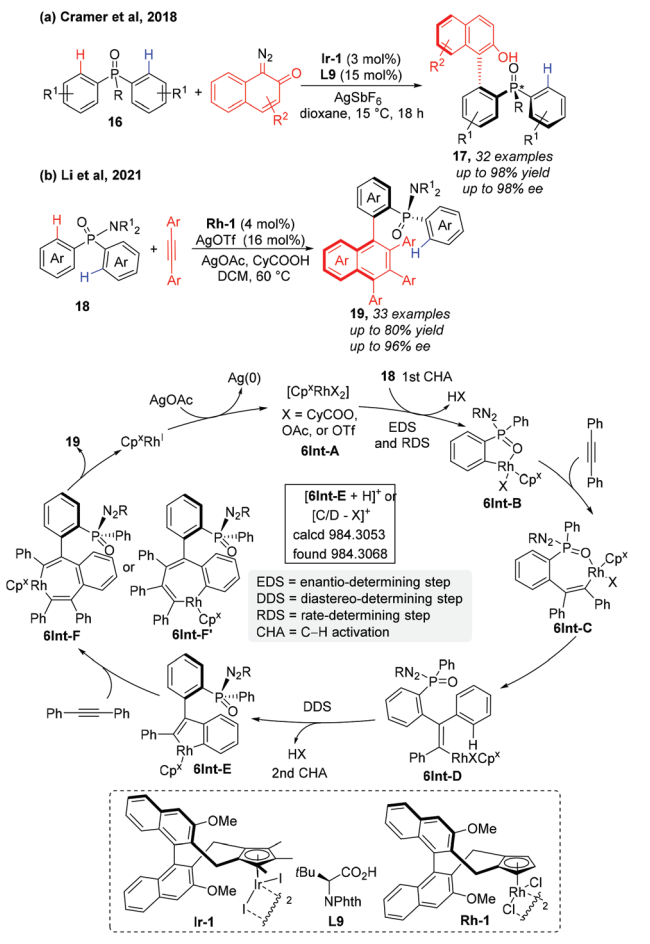


Scheme 5 Pd(II)-Catalyzed enantioselective intermolecular *meta*-C(sp^2)–H arylation.

reacted smoothly, giving the desired chiral products in good yields with high enantioselectivity.

In 2018, Cramer and coworkers reported a chiral $Cp^xIr(III)$/CCA **L9** catalyzed enantioselective C–H arylation of phosphine oxides **16** with *o*-quinone diazides, allowing the generation of desired products containing both a biaryl backbone and *P*-chiral biaryl phosphine oxides (Scheme 6a).[18a] Although a chiral $Cp^xIr(III)$ was employed, the stereocontrol ability of C–H activation still needs to be enhanced by the cooperative effect of CCA **L9**. Furthermore, the enantiospecific reduction of the product gives access to chiral P(III) compounds, providing an alternative approach for the synthesis of chiral biaryl monophosphines which could be used as ligands in asymmetric catalysis.

Later in 2021, Li and coworkers reported a chiral $Cp^xRh(III)$-catalyzed twofold C–H activation/annulation for the enantio- and diastereoselective C–H synthesis of biaryls bearing both a *P*-stereogenic center and axial chirality (Scheme 6b).[18b] Chiral $Cp^xRh(III)$ was used as the only chirality source and diarylacetylenes were employed as the arylating reagents. Based on mechanistic studies, a possible reaction pathway is proposed in Scheme 6b. The reaction is initiated by carboxylate-assisted,



Scheme 6 Chiral $Cp^xM(III)$/CCA-catalyzed asymmetric $C(sp^2)$–H arylation of phosphine oxides.

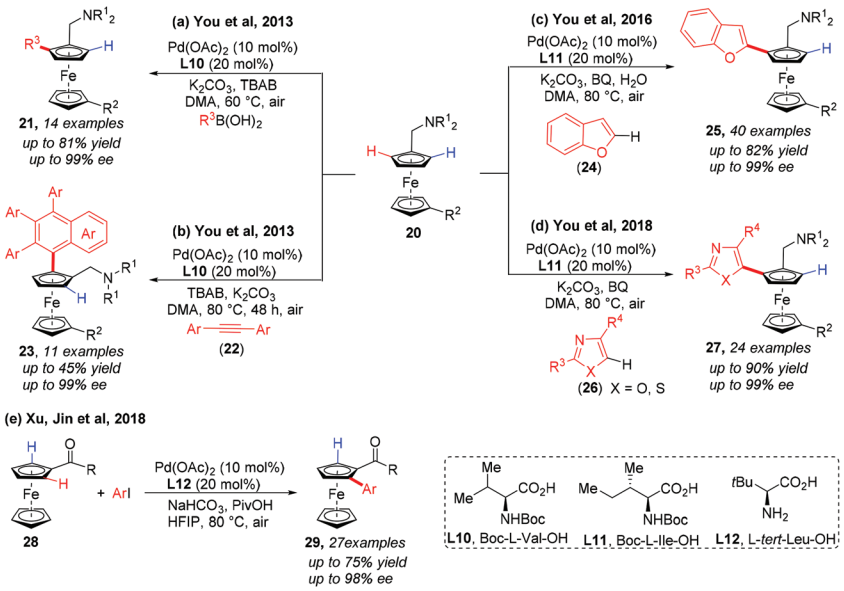
enantio-determining C–H activation to form the rhodacyclic intermediate **6Int-B**. The insertion of diphenylacetylene resulted in a rhodacycle **6Int-C**, followed by *cis–trans* isomerization of the Rh^{III} alkenyl moiety to give birth to **6Int-D**. Then, a stable rhodacyclic intermediate **6Int-E** was obtained through a diastereo-determining C–H activation of **6Int-D**. The second alkyne insertion into **6Int-E** gave **6Int-F** or **6Int-F′**, which underwent C–C reductive elimination to release the desired product **19**. Finally, the Rh^I catalyst was oxidized to Rh^{III} and closed the catalytic cycle. The practicality of this reaction was demonstrated by the scaled-up reaction and the transformation of the product to a chiral phosphorus ligand which was applied in palladium-catalyzed asymmetric allylic alkylation of an allyl acetate.

Enantioselective desymmetric C–H functionalization has also been applied in the construction of planar chirality since the pioneering work by the You group.[19,20] In 2013, a Pd(II)-catalyzed enantioselective desymmetric C–H arylation of ferrocenes with aryl boronic acids was developed by You, Gu and coworkers (Scheme 7a).[20a] A wide variety of aryl boronic acids were well tolerated, giving planar chiral ferrocenes **21** in good to excellent yields with excellent enantioselectivities by the use of commercially available Boc-L-Val-OH **L10** as a chiral ligand and O_2 as the oxidant. Unfortunately, aliphatic boronic acid was unsatisfactory, giving the corresponding product in 14% yield only, even under higher temperature. Noteworthily, this is the first example for the synthesis of planar chiral ferrocenes *via* Pd(II)-catalyzed asymmetric C–H functionalization. Later, the same group achieved the Pd(II)-catalyzed enantioselective C–H annulation of ferrocenes with diarylethynes using Boc-L-Val-OH **L10** as the chiral ligand. The desired products **23** were generated in moderate yields with excellent enantioselectivities (Scheme 7b).[20b]

In 2016, the You group realized a Pd(II)-catalyzed regio- and enantioselective oxidative C–H/C–H cross-coupling reaction between ferrocenes and heteroarenes using a similar catalytic system (Scheme 7c).[20c] Oxygen was used as the oxidant and Boc-L-Ile-OH **L11** was used as the chiral ligand. A variety of heteroarenes, such as benzofurans, thiophenes, pyrroles, and indoles, were tolerated and gave the corresponding products **25** in good yields with excellent enantioselectivities. Later, they also demonstrated the asymmetric oxidative C–H cross-coupling reaction between ferrocenes with azoles, such as oxazoles and thiazoles (Scheme 7d).[20d] Deuteration experiments suggested that C–H bond cleavage of oxazole likely proceeds through a S_EAr process and may not be a turnover limiting step but the C–H bond cleavage of ferrocenes may be the rate-limiting step.

In 2018, Xu, Jin and coworkers developed a Pd-catalyzed enantioselective arylation of ferrocenyl ketones using L-*tert*-leu-OH **L12** as a chiral transient directing group (Scheme 7e).[21,22] It is worth noting that the arylated products could be easily converted into other new planar chiral ferrocene mono-phosphine ligands, which were successfully applied in asymmetric annulation reaction.

In 2019, a new catalytic system was developed by You and coworkers in which the $[Rh(C_2H_4)_2Cl]_2$ and TADDOL-derived



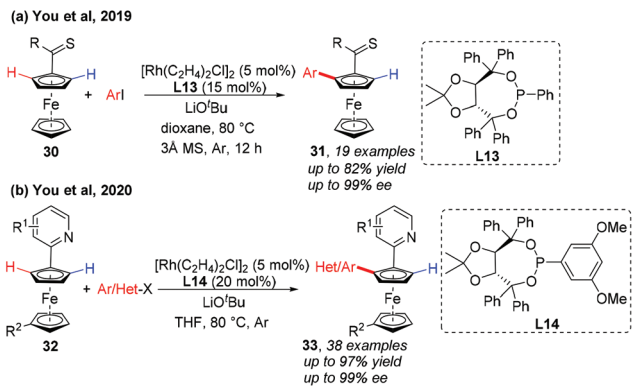
Scheme 7 Pd(II)-Catalyzed enantioselective intermolecular C–H arylation of ferrocenes.

monophosphonite was applied as the catalyst and chiral ligand respectively. Thioketone was found to be an efficient directing group in the enantioselective desymmetric C–H bond arylation of ferrocenes (Scheme 8a).[23] Under optimized conditions, a variety of planar chiral ferrocene derivatives **31** were synthesized in moderate to good yields with good to high enantioselectivities. Later, they successfully expanded this catalytic system to the use of pyridine as directing group (Scheme 8b).[24] Notably, the reaction could be conducted with low catalyst loading (1 mol% rhodium catalyst), which greatly enhanced the practicality of the reaction.

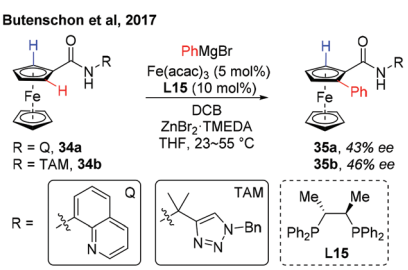
In 2017, an example of Fe-catalyzed enantioselective C–H arylation of ferrocene bearing bidentate directing groups with phenylmagnesium bromide using (*R*,*R*)-Chiraphos **L15** was reported by Butenschön and coworkers. When 8-aminoquinoline was used as the directing group, the arylated planar-chiral ferrocene **35a** was obtained in 43% ee. Switching to triazole-containing bidentate auxiliary led to slightly improved enantioselectivity (Scheme 9, **35b**, 46% ee).[25]

2.3 Alkenylation

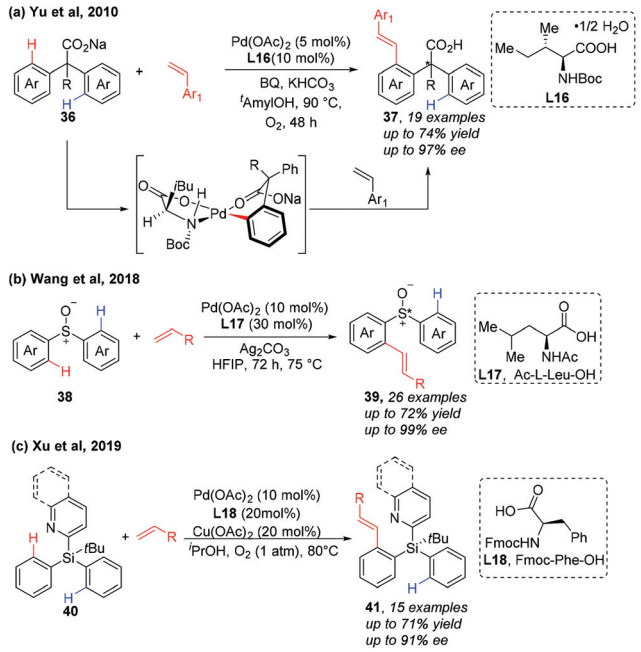
In 2010, Yu and coworkers demonstrated another application of the Pd(II)/MPAA system in a Pd(II)-catalyzed enantioselective C(sp^2)–H olefination reaction (Scheme 10a).[26] In this catalysis, Boc-L-isoleucine **L16** was used as the ligand and a simple carboxylate was used as the directing group. The mode of enantiocontrol was the same as that described in Scheme 1. Later in 2018, a similar catalytic system was explored by the Wang group for the construction of sulfur chiral centers (Scheme 10b).[27a] A variety of symmetric and non-symmetric substrates were converted into the desired chiral olefinated products **39** in good yields and high enantioselectivities through both desymmetrization and the parallel kinetic resolution (PKR) pathway. In 2019, the Pd(II)/MPAA catalytic system was expanded to the synthesis of silicon stereogenic center by Xu and coworkers *via* a Pd-catalyzed, pyridine- or quinoline-directed enantioselective C–H olefination of diaryl-substituted tetraorganosilicon derivatives **40** (Scheme 10c).[27b] The use of



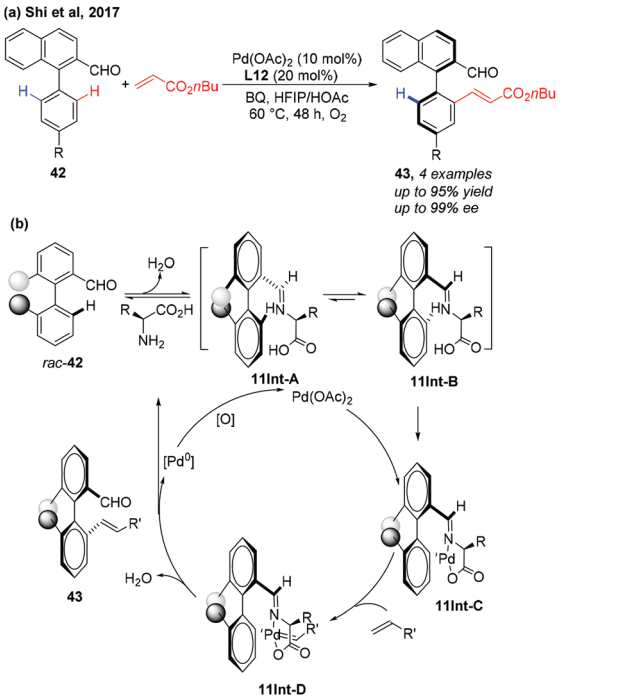
Scheme 8 Rh(I)-Catalyzed enantioselective intermolecular C–H arylation of ferrocenes.



Scheme 9 Fe-Catalyzed enantioselective intermolecular C–H arylation of ferrocenes.



Scheme 10 Pd(II)-Catalyzed enantioselective intermolecular C(sp^2)–H alkenylation.



Scheme 11 Pd(II)-Catalyzed asymmetric C(sp^2)–H olefination of biphenyls by chiral transient directing group.

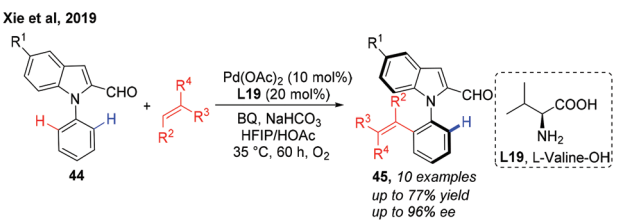
Fmoc-Phe-OH **L18** as the chiral ligand enables the formation of nitrogen-containing silicon-stereogenic tetraorganosilicon products in moderate yields and good to excellent enantioselectivities.

Enantioselective desymmetric C–H functionalization is also a valuable strategy for the construction of axial chirality.[28] In 2017, Shi and coworkers reported a Pd-catalyzed asymmetric C–H olefination for the synthesis of axially chiral biaryls using L-*tert*-leu-OH **L12** as the transient chiral auxiliary (Scheme 11a).[29] Excellent yields and enantioselectivities (up to 99% ee) were observed for various prochiral biaryl substrates. A plausible reaction mechanism is depicted in Scheme 11b. Firstly, a mixture of diastereoisomer imines **11Int-A** and **11Int-B** might be generated through the reversible reaction of chiral amino acid with biaryl aldehydes. Then, the C–H cleavage of one diastereomer (**11Im-B**) is preferred to give an axially stereoenriched biaryl palladacycle **11Int-C** because of the steric interaction, followed by a Heck-type reaction with an olefin to afford **11Int-D**. Finally, hydrolysis of **11Int-D** would afford the axially chiral biaryl aldehyde **43**. Reoxidation of Pd(0) to Pd(II) species by BQ and O_2 closed the catalytic cycle. Shi coworkers further successfully extended the chiral transient directing group strategy to Pd(II)-catalyzed atroposelective C–H alkynylation/allylation/naphthylation of prochiral biaryl aldehydes, affording the desired axially chiral biaryls in good to high yields and excellent enantioselectivities with **L12** as a key catalytic transient chiral auxiliary.[30]

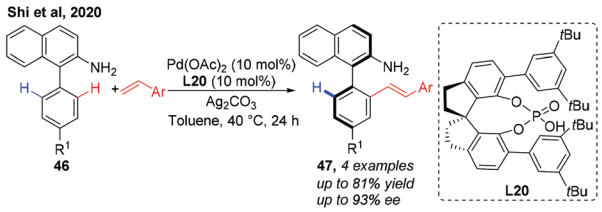
The construction of atropoisomers featuring pentatomic heteroaromatics is more difficult than of biaryls containing hexatomic aromatics due to the increased distance of substituents *ortho* to the axis, which is responsible for lower barriers of rotation.[31] In 2019, Xie and coworkers expanded this chiral transient directing group strategy to access N–C axial chirality by Pd(II)-catalyzed atroposelective C–H olefination/desymmetrization of *N*-arylindoles **44** using L-valine **L19** as the transient chiral auxiliary. Various N–C axially chiral *N*-aryl indoles **45** were afforded in moderate to good yields with excellent enantiocontrol (Scheme 12).[32]

Chiral spiro phosphoric acids (SPAs) were first used as a type of efficient chiral ligands in Pd-catalyzed C–H activation reactions by Shi and coworkers in 2019.[33] Recently, they demonstrated the highly efficient synthesis of axially chiral biaryl-2-amines by Pd-catalyzed atroposelective C–H olefination using SPA **L20** as the chiral ligand (Scheme 13).[34] Notably, free amine was used as the directing group, giving a variety of chiral biaryl-2-amines in good yields with high enantioselectivities.

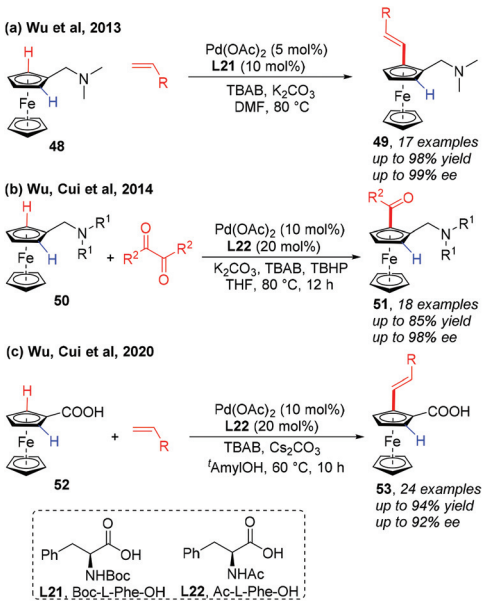
In 2013, Wu, Cui and coworkers independently reported the Pd(II)-catalyzed enantioselective desymmetric C–H olefina-



Scheme 12 Pd(II)-Catalyzed asymmetric C(sp^2)–H olefination of *N*-arylindoles.



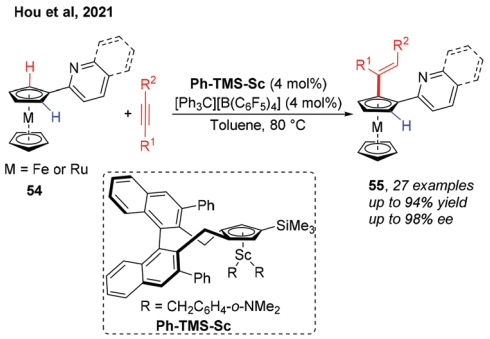
Scheme 13 Pd(II)-Catalyzed atroposelective C(sp^2)–H olefination of biaryl-2-amines.



Scheme 14 Enantioselective intermolecular C–H alkenylation and acylation of ferrocenes.

tion of ferrocenes **48** with terminal olefins using Boc-L-Phe-OH **L21** as the chiral ligand (Scheme 14a).[35] In 2014, Wu's group further extended the application of this catalytic system, realizing an enantioselective C–H acylation of ferrocene derivatives with diaryl diketones using Ac-L-Phe-OH **L22** as the chiral ligand. However, dramatically decreased enantioselectivities of acylation ferrocene was observed when dialiphatic diketones were employed (Scheme 14b).[36] In 2020, a Pd(II)-catalyzed enantioselective C–H alkenylation of weakly coordinated ferrocenecarboxylic acid using Ac-L-Phe-OH as the chiral ligand was reported by the same group (Scheme 14c).[37]

Very recently, the Hou group synthesized a chiral half-sandwich scandium catalyst **Ph-TMS-Sc**, which was employed in an enantioselective C–H alkenylation of ferrocenes with internal alkynes to synthesize various *N*/alkene-functionalized planar chiral ferrocenes **55** in high yields with excellent enantioselectivities (Scheme 15).[38] The deuterium-labelling experiments suggested that C–H activation could also take place at the C8 position of quinoline moiety, even though the alkyne insertion only occurred at the Cp ring of ferrocene. The practicality of this catalysis was demonstrated by employing the *N*/



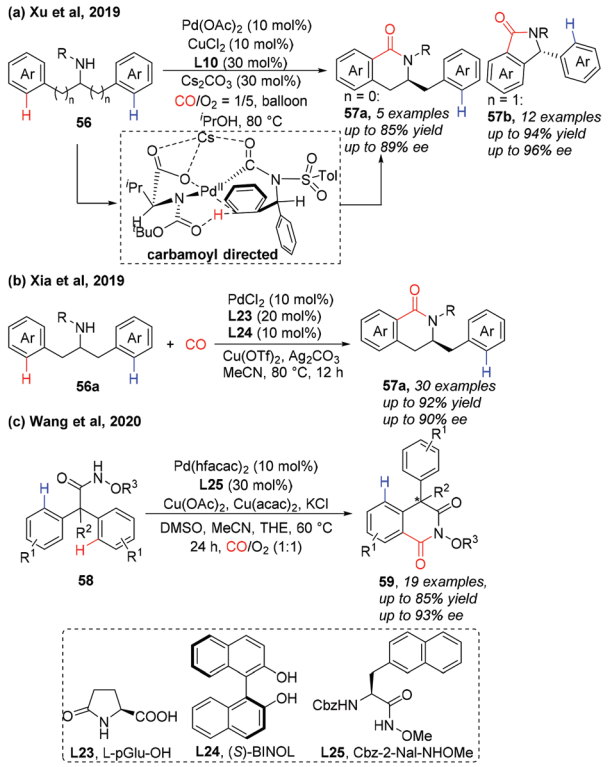
Scheme 15 Enantioselective intermolecular C–H alkenylation of ferrocenes.

alkene-functionalized product as an efficient chiral ligand in Rh-catalyzed asymmetric 1,4-addition of an aryl boric acid to cyclohexanone.

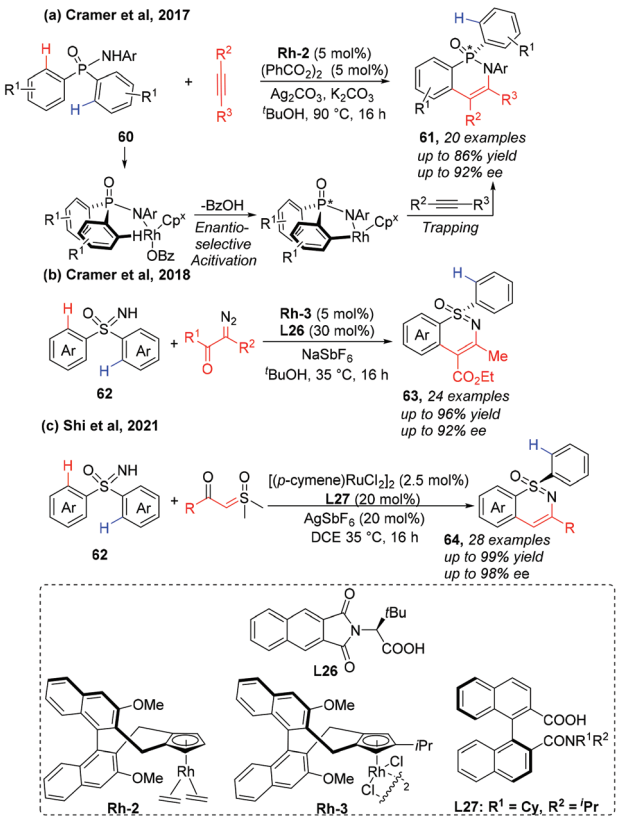
2.4 Annulation

MPAAs have been successfully applied in various Pd(II)-catalyzed asymmetric C–H activation reactions, since the first example was discovered by the Yu group in 2008.[10] In 2019, Xu and coworkers employed Boc-L-Val-OH **L10** as a ligand in a Pd/Cu-catalyzed enantioselective desymmetric oxidative C–H/N–H carbonylation of diarylsulfonamides **56a** and diarylmethylsulfonamides **56b** (Scheme 16a).[39a] With this methodology, diverse chiral isoindoline-1-ones **57a** and isoquinoline-1-ones **57b** were formed in good yields and enantioselectivities. Interestingly, DFT calculations suggested that C–H activation was directed by the carbamoyl group rather than the amine group. At the same time, Xia, Lan and coworkers reported a Pd-catalyzed enantioselective C–H aminocarbonylation of secondary amines using L-pyroglutamic acid **L23** as the chiral ligand. A range of chiral isoquinolinones **57a** were obtained in good yields with high enantioselectivities (Scheme 16b).[39b] DFT calculations indicated that the use of a catalytic amount of (*S*)-BINOL **L24** plays a crucial role in stabilizing the Pd(0) intermediate, avoiding the catalyst deactivation and improving the yield significantly. KIE experiments suggested that C–H activation might be involved in the rate-determining step. In 2020, the Wang group modified the MPAA ligands to synthesize a variety of mono-*N*-protected α-amino-*O*-methylhydroxamic acids (MPAHAs), which enabled the Pd(II)-catalyzed asymmetric C–H carbonylation/C–N formation of *N*-methoxy-2,2-diphenylpropanamides **59** (Scheme 16c).[40]

In 2017, Cramer and coworkers successfully realized the construction of *P*-chiral cyclic phosphinamides *via* a chiral Cp^xRh(III)-catalyzed enantiotopic C–H annulation with alkynes (Scheme 17a).[41] Compared with the Cp^xRh(III) catalyst, the sterically hindered chiral Cp^xRh(III) complex could not only control the enantioselectivities effectively but also exhibit outstanding regioselectivities for unsymmetrical alkynes. Later in 2018, the same research group synthesized a new chiral Cp^xRh(III) catalyst and used it in the chiral Cp^xRh(III)/CCA-catalyzed asymmetric C–H cyclization of sulfoximines (Scheme 17b).[42a]



Scheme 16 Pd-Catalyzed enantioselective C(sp^2)–H carbonylation.



Scheme 17 Asymmetric annulation of phosphinamides and sulfoximines.

At almost the same time, the Li group independently reported an enantiodivergent reaction of sulfoximines with a range of diazo compounds *via* chiral Cp^{x}Rh(III)-catalyzed desymmetrizing annulation by the judicious choice of achiral carboxylic acids with different steric biases.[42b]

Very recently, the Shi group revealed a new catalytic system, [(*p*-cymene)$RuCl_2$]$_2$ and CCA **L26**, which was successfully used in asymmetric C–H annulation of sulfoximines with α-carbonyl sulfoxonium, delivering diverse chiral sulfoximines **63** in high yields with excellent enantioselectivities (Scheme 17c).[43] Compared to the synthesis of chiral Cp^{x}Rh(III) that are normally used in this kind of reaction, the binaphthyl monocarboxylic acid **L27** was much easier to access. Furthermore, this is also the first example of Ru-catalyzed asymmetric C–H functionalization reactions proceeding through an enantiodetermining C–H cleavage. The significance of this catalytic system was also proved by the high reactivity and enantiocontrol in kinetic resolution, and parallel kinetic resolution reactions.

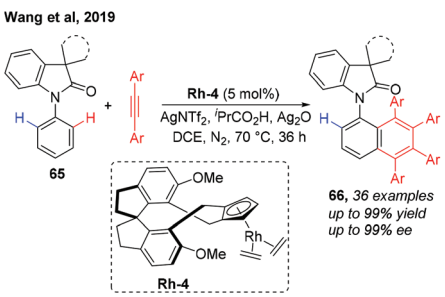
In 2019, Wang and coworkers employed the chiral rhodium (III) catalyst **Rh-4** in a dual C–H activation strategy for the asymmetric construction of C–N axial chirality (Scheme 18a).[44] The process generates the desired chiral *N*-aryloxindoles **66** in high yields and enantioselectivities. Notably, it is the first example of the asymmetric synthesis of C–N axial chirality *via* an enantioselective Satoh–Miura-type reaction.

2.5 Lactonization

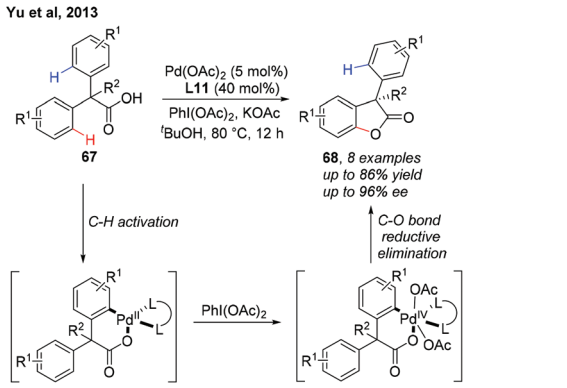
In 2013, Wang, Yu and coworkers presented the first example of a Pd(II)/Pd(IV) redox catalysis in enantioselective intramolecular C–O bond formation using Boc-L-Ile-OH **L11** as the chiral ligand (Scheme 19).[45] $PhI(OAc)_2$ was used as the oxidant to enable the oxidation of the Pd(II) metallacycle to a Pd(IV) cyclometalated intermediate, which could facilitate the subsequent C–O reductive elimination. An array of chiral benzofuranones were efficiently synthesized in good yields with high enantioselectivities.

2.6 Iodination

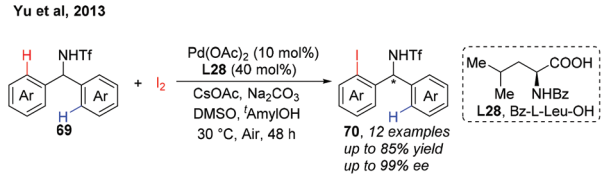
In 2013, Yu and coworkers expanded the application of MPAAs into a Pd(II)-catalyzed enantioselective C–H iodination reaction for the construction of chiral diarylmethylamines using I_2 as a



Scheme 18 Chiral Cp^{x}Rh-catalyzed asymmetric construction of C–N axial chirality.



Scheme 19 Pd(II)-Catalyzed enantioselective intramolecular C–O formation.



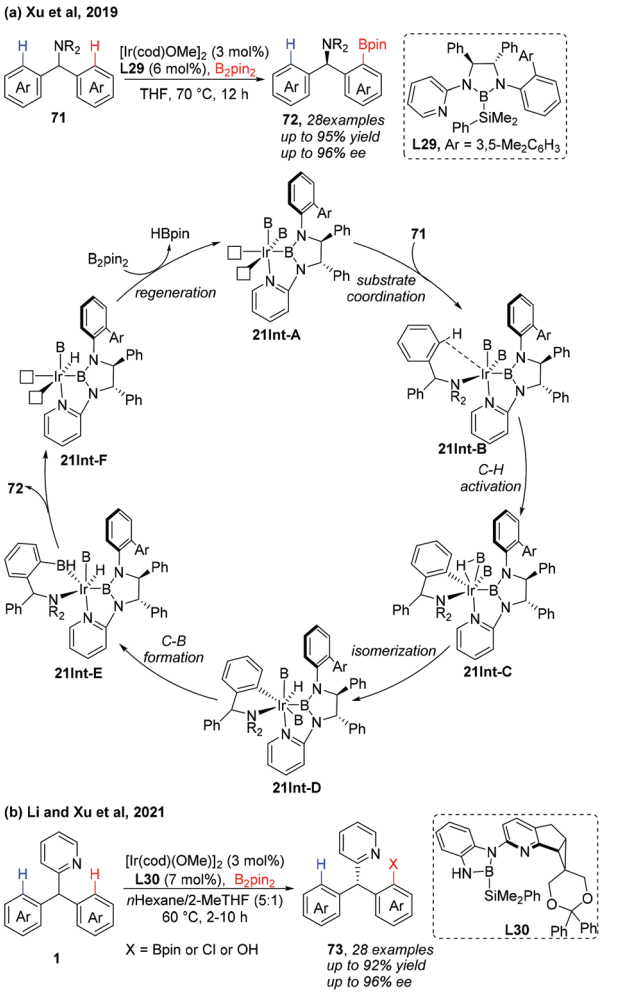
Scheme 20 Pd(II)-Catalyzed enantioselective C(sp^2)–H iodination.

practical halogenating reagent (Scheme 20).[46] Noteworthily, the resulting products bearing an iodine residue could undergo various transformations providing a new approach to prepare diarylmethylamine analogues.

2.7 Borylation

Chiral organoboron compounds are an important class of building blocks in organic synthesis due to their unique reactivity and versatility. Therefore, transition-metal-catalyzed enantioselective C–H borylation has drawn much attention in the last few years.[47] Enantioselective C–H borylation initiated by Si–H insertion has been well reviewed recently and will not be discussed in this review.[9e–h,47,48]

In 2019, the Xu group designed a novel type of chiral bidentate *B*,*N*-ligands which were used in an Ir-catalyzed asymmetric C(sp^2)–H borylation reaction using tertiary amine as the directing group (Scheme 21a).[49] This catalytic system enables not only the desymmetrization of prochiral diarylmethylamines but also kinetic resolution of racemic diarylmethylamines. The resulting C–B bonds could be further converted into various important functionalities. Based on the DFT calculations, a proposed mechanism was given in Scheme 21a. The reaction initiates with the formation of 14-electron two-vacant-site Ir(III) active species **21Int-A** from the precatalyst $[IrCl(COD)]_2$, a ligand and B_2pin_2. The coordination of **21Int-A** with diarylmethylamine **71** and subsequent C–H activation gave birth to the chiral seven-coordinate Ir(V) intermediate **21Int-C** which isomerized to a thermodynamically stable intermediate **21Int-D** with lower Gibbs free energies. **21Int-D** undergoes reductive elimination to release the borylated product

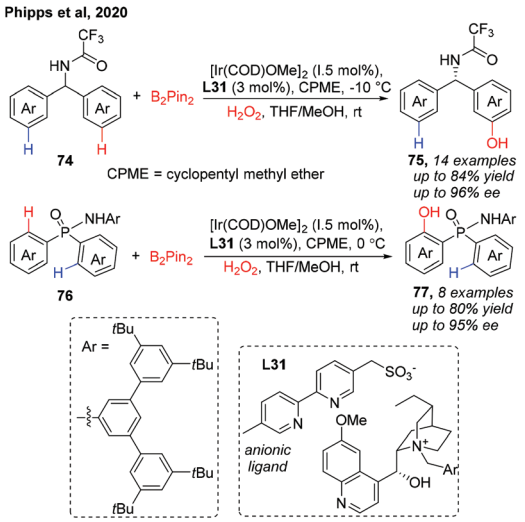


Scheme 21 Ir(I)-Catalyzed enantioselective C(sp^2)–H borylation using *B*,*N*-ligands.

and the active catalyst **21Int-A** is regenerated in the presence of B_2pin_2.

Very recently, Li, Xu and coworkers reported the Ir-catalyzed asymmetric C–H borylation of diphenyl(2-pyridyl)methane **1** using *B*,*N*-bidentate ligand **L30** bearing a chiral pyridine unit (Scheme 21b).[50] The borylated products **73** were obtained in high yields and enantioselectivities (up to 96% ee and 93% yield). The resulting borylation products could be easily transformed into various chiral tri(hetero)arylmethane compounds.

In 2020, an unprecedented enantioselective desymmetrization of the geminal diaryl motif *via* Ir-catalyzed remote C–H borylation reaction has been developed by Phipps and coworkers (Scheme 22).[51] Based on their previous studies,[52] an Ir(I)/anionic ligand/chiral cation catalytic system was developed, giving the *meta*-borylated products containing carbon or phosphorus stereocenters in high yields and enantioselectivities. A bipyridine ligand **L31** bearing an anionic sulfonate group can not only coordinate with the iridium catalyst for regioselective C–H activation but also pair with privileged chiral cations to control the enantioselectivity. Notably, this catalysis opened a



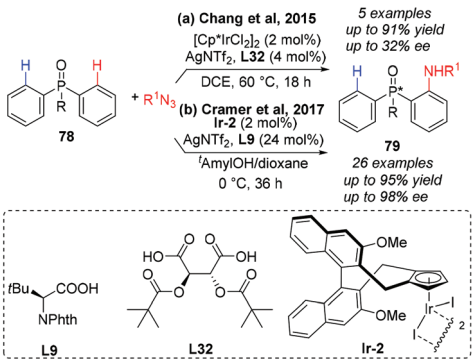
Scheme 22 Ir(I)-Catalyzed enantioselective C(sp^2)–H borylation of geminal diaryl motif.

brand new area for the application of chiral cations in transition-metal-catalyzed asymmetric C–H activation.

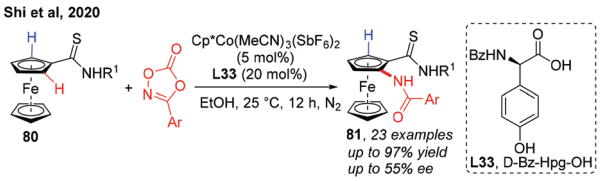
2.8 Amidation

In 2015, Chang and coworkers revealed a dual role of a carboxylic acid additive for the Cp^xIr(III)-catalysed asymmetric C–H amidation of arylphosphoryl compounds although only low enantioselectivities were obtained using the *O*,*O*-dipivaloyl-L-tartaric acid **L32** as the chiral ligand (Scheme 23a).[53] Shortly thereafter, Cramer and coworkers achieved the highly enantioselective C(sp^2)–H amidation of arylphosphoryl compounds **78** by the combination of the chiral Cp^xIr(III) catalyst (**Ir-2**) and *N*-phthaloyl-Tle-OH (**L9**). The amidated *P*-chiral arylphosphine oxides were obtained in excellent yields and enantioselectivities (Scheme 23b).[54] Notably, a very strong cooperative effect between the chiral Cp^x catalyst and *N*-phthaloyl-Tle-OH was crucial for the enantioselectivity.

Recently, Shi and coworkers reported an achiral Cp^xCo(III)-catalyzed enantioselective C–H amidation of ferrocenes using



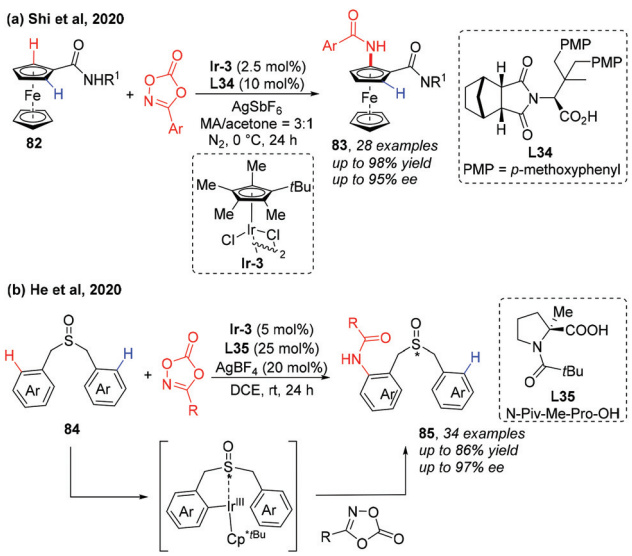
Scheme 23 Cp*Ir(III)-Catalyzed enantioselective C(sp^2)–H amidation of diarylphosphine oxides.



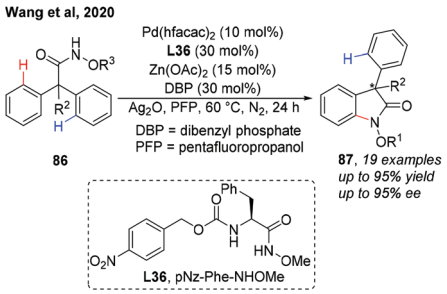
Scheme 24 Cp*Co-Catalyzed enantioselective intermolecular C–H amidation of ferrocenes.

D-Bz-Hpg-OH **L33** as the chiral ligand, giving the desired products in good yields with moderate enantioselectivities (Scheme 24).[55] Notably, the planar chiral aminated ferrocene could be obtained in excellent optical purity after recrystallization.

Inspired by their previous work on the synthesis of amino acids and peptides with bulky side chains *via* C–H arylation,[56] Shi and coworkers successfully synthesized a novel type of α-amino acids bearing sterically bulky side chains, which were used as chiral ligands in achiral Cp^xIr(III)-catalyzed enantioselective C–H amidation of ferrocene carboxamides under mild conditions (Scheme 25a).[57] The success of this reaction relied on the choice of chiral carboxylic acid **L34** derived from L-*tert*-leu-OH, which could be prepared by one-step C(sp^3)–H arylation. Achiral Cp^xIr(III)-catalyzed asymmetric C–H amidation for the construction of a sulfur chiral center was reported by the He group independently (Scheme 25b).[58] A modified chiral proline **L35** (***N*-Piv-Me-Pro-OH**) was utilized as the chiral ligand to obtain the desired products with high yields and excellent enantioselectivities. Furthermore, the amidated sulfoxides were converted to a variety of *S*,*N*-bidentate and *S*,*N*,*X*-tridentate (*X* = N, O, P) chiral ligands, which could be used in asymmetric synthesis.

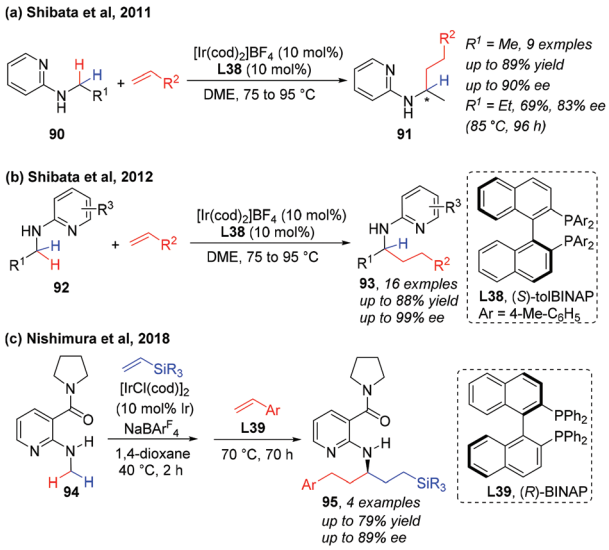


Scheme 25 Ir(III)-Catalyzed enantioselective intermolecular C–H amidation of ferrocenes.



Scheme 26 Pd-Catalyzed enantioselective intramolecular C–H amidation.

In 2020, the Wang group expanded the application of mono-*N*-protected α-amino-*O*-methylhydroxamic acids (MPAHAs) in a Pd-catalyzed C(sp^2)–H amination of *N*-methoxy-2,2-diphenylpropanamide for the synthesis of diverse nitrogen-containing heterocycles **87** in moderate to good yields and high enantioselectivities (Scheme 26).[59]



Scheme 28 Ir(I)-Catalyzed enantioselective C(sp^3)–H alkylation.

3. Desymmetric C(sp^3)–H functionalization

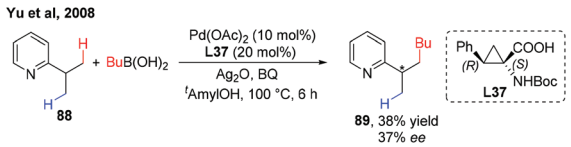
3.1 Desymmetric C(sp^3)–H functionalizations of acyclic compounds

3.1.1 Alkylation. In their pioneering study on Pd(II)-catalyzed enantioselective alkylation of C(sp^2)–H bond *via* a Pd(II)/Pd(0) catalysis using MPAA as the chiral ligand by Yu and coworkers, an example of the desymmetric C(sp^3)–H alkylation of *gem*-dimethyl was demonstrated (Scheme 27).[10] *N*-Boc protected cyclopropane amino acid **L37** was found to be the optimal chiral ligand, leading to the formation of the chiral alkylated product **89** in 38% yield with 37% ee. Although the enantioselectivity was relatively low, this proof-of-concept result paved the way for the development of enantioselective desymmetric C(sp^3)–H functionalization reactions.

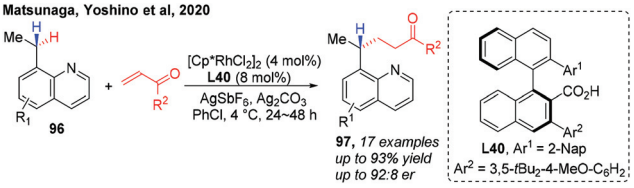
In 2011, Shibata and coworkers reported the first cationic Ir(I)/(*S*)-tolBINAP complex catalyzed enantioselective C(sp^3)–H alkylation of 2-(ethylamino)pyridine with styrenes, giving the desired chiral amines **91** in good yields with high enantioselectivities (Scheme 28a).[60] Preliminary studies revealed that 1-phenyl-buta-1,3-diene was also compatible with this protocol, leading to the formation of unsaturated chiral amine only in the *E*-form with high enantiocontrol. 2-(Propylamino)pyridine was also tolerated, affording the alkylated product in comparable yield and enantioselectivity under a prolonged reaction time (96 h). In 2012, they further investigated the directing ability of nitrogen-containing heteroarenes other than pyridine under the same reaction conditions and found that quinoline and pyridine were the best directing groups. The scope of alkenes was also examined and extended to ethyl acrylate, vinylsilanes and allylsilanes (Scheme 28b).[61] Interestingly, enantioselective C(sp^3)–H alkenylation could also be achieved under elevated temperature with prolonged reaction time (135 °C, 18.5 h), albeit in low yield (32%, 89% ee).

In 2018, Nishimura and coworkers developed an Ir(I)-catalyzed sequential C(sp^3)–H alkylation of an *N*-methyl group with two different alkenes, leading to the formation of α-substituted chiral amines using (*R*)-BINAP as the chiral ligand (Scheme 28c).[62] Notably, the use of vinylsilanes as the first alkylation reagents would ensure selective monoalkylation.

Recently, the Matsunaga group developed a Cp^xRh(III)/binaphthyl-based CCA (**L40**) catalyzed enantioselective methylene C(sp^3)–H alkylation of 8-alkylquinolines with α,β-unsaturated carbonyl compounds (Scheme 29).[63] Mechanistic studies indicate that CCA **L40** is mainly responsible for the enantioselective C–H activation to irreversibly generate chiral metallacycle intermediate, which is consistent



Scheme 27 Pd(II)-Catalyzed enantioselective desymmetric C(sp^3)–H alkylation.



Scheme 29 Cp*Rh(III)-Catalyzed enantioselective C(sp^3)–H alkylation.

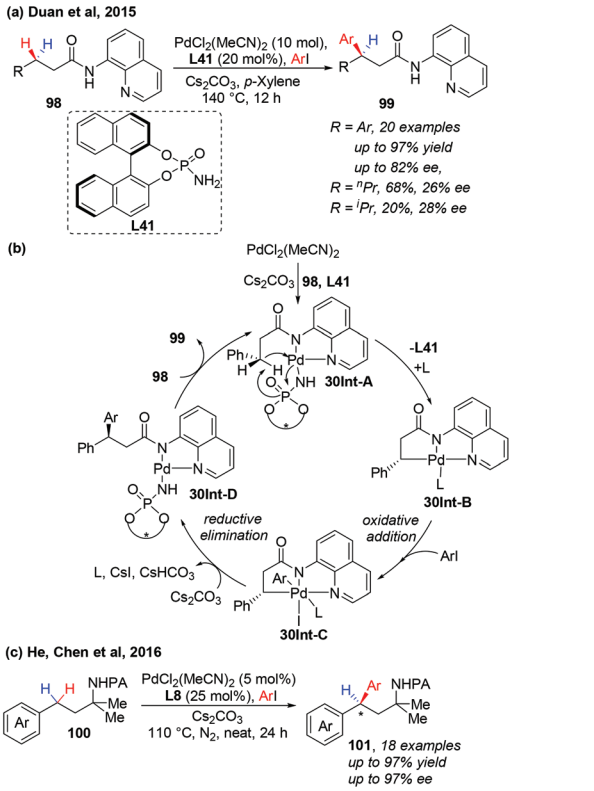
with their previous studies in Rh(III)/CCA-catalyzed asymmetric C(sp^3)–H amidation (Section 3.1.6, Scheme 44a).[64]

3.1.2 Arylation and alkenylation. In 2015, Duan and coworkers first reported an 8-aminoquinoline directed, Pd(II)-catalyzed asymmetric arylation of benzylic methylene C(sp^3)–H bond with aryl iodines using chiral phosphoric amide **L41** as the ligand, providing the arylated products in moderate enantioselectivities (Scheme 30a, up to 82% ee).[65] Unfortunately, relatively low yields and enantioselectivities were obtained when more challenging aliphatic amides bearing alkyl substituents were used as substrates (R = ^{n}Pr, 68%, 26% ee; R = ^{i}Pr, 20%, 28% ee). A proposed mechanism is shown in Scheme 30b. The reaction initiates with the coordination of $PdCl_2(CH_3CN)_2$ with substrate **98** in the presence of Cs_2CO_3 and chiral phosphoric amide **L41** leads to a Pd(II) intermediate **30Int-A**. The asymmetric cleavage of methylene C(sp^3)–H gave the chiral palladacycle intermediate **30Int-B**, which underwent oxidative addition with iodoarene to give the Pd(IV) intermediate **30Int-C**. Then, reductive elimination of intermediate **30Int-C** gave the arylated intermediate **30Int-D**. Finally, the corresponding arylated product **99** was generated after ligand exchange with substrate **98**.

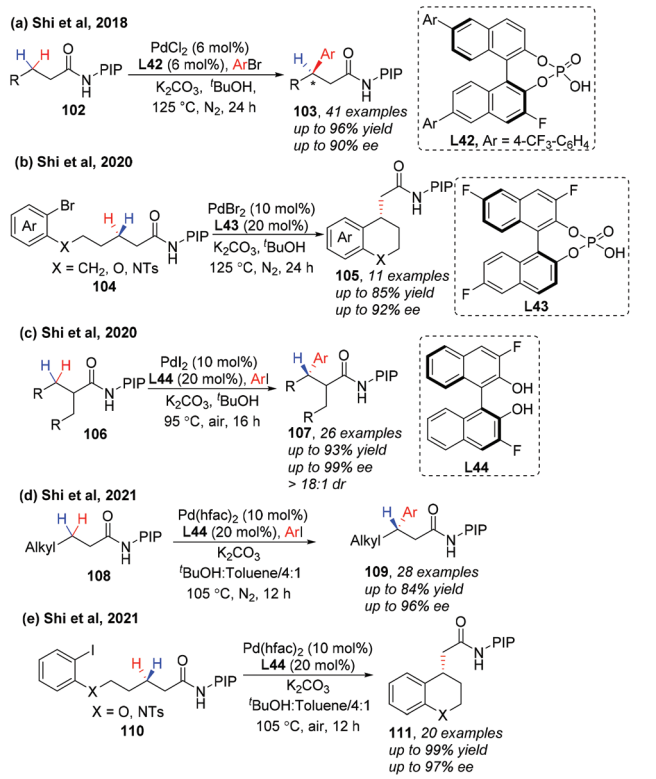
Inspired by this seminal work, He, Chen and coworkers reported a picolinamide-directed, Pd(II)-catalyzed asymmetric benzylic methylene C(sp^3)–H arylation reaction (Scheme 30c).[66] Utilizing chiral phosphoric acid **L8** instead of the chiral phosphoric amide **L41** improved both the reactivity and enantioselectivity, giving γ-arylated products in up to 97% yield with up to 97% ee under solvent-free conditions. A nonlinear effect was observed, indicating that more than one ligand might be involved in the enantio-determining C–H cleavage step.

The abovementioned Pd(II)-catalyzed enantioselective methylene C(sp^3)–H arylation reactions were limited to the cleavage of relatively activated benzylic C–H bonds. To overcome this limitation, the Shi group reported the Pd(II)-catalyzed enantioselective arylation of unbiased methylene C(sp^3)–H bonds with less reactive aryl bromides directed by their self-developed 2-pyridinylisopropyl (PIP) bidentate auxiliary (Scheme 31a).[67] Interestingly, the non-C_2-symmetric CPA **L42** was found to be crucial for high stereocontrol. A wide range of aliphatic amides and aryl bromides were well tolerated, giving the β-arylated aliphatic amides in high yields with good enantioselectivities (up to 96% yield and 90% ee). The Pd(II)/non-C_2-symmetric CPA catalytic system was further extended to a PIP-directed intramolecular version. A variety of chiral benzo-ring containing compounds were prepared using **L43** as the chiral ligand (Scheme 31b).[68]

In 2019, the Shi group developed a Pd(II)/3,3′-F_2-BINOL-catalyzed enantioselective alkynylation of unbiased methylene C(sp^3)–H bonds with alkynyl bromides directed by a PIP bidentate auxiliary.[69] Inspired by this work, they achieved the first Pd-catalyzed enantioselective desymmetric C(sp^3)–H arylation



Scheme 30 Pd(II)-Catalyzed enantioselective arylation of benzylic methylene C(sp^3)–H bonds.



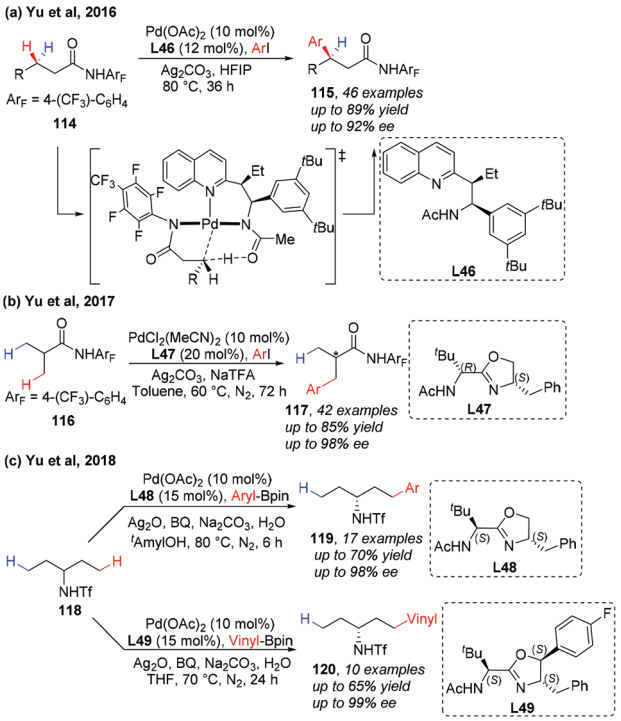
Scheme 31 Pd(II)-Catalyzed enantioselective arylation of unbiased methylene C(sp^3)–H bonds directed by PIP bidentate auxiliary.

of α-*gem*-dialkyl acyclic amides in 2020 (Scheme 31c).[70] The combination of PIP auxiliary and 3,3′-F_2-BINOL **L44** was crucial for overcoming the chemo- and stereocontrol problems caused by the four chemically identical unbiased methylene C(sp^3)–H bonds, delivering acyclic aliphatic amides with α,β-contiguous stereogenic centers in high yields and good enantio-, chemo- and diastereoselectivity. The Pd(II)/3,3′-F_2-BINOL catalytic system was successfully used in the enantioselective and intermolecular arylation of unbiased methylene C(sp^3)–H bonds using aryl iodides as the arylation reagents (Scheme 31d and e).[71]

In 2020, Shi and coworkers reported the synthesis of β-stereogenic γ-lactams *via* a Pd-catalyzed tandem enantioselective methylene C(sp^3)–H alkenylation/aza-Wacker cyclization using chiral 3,3′-F_2-BINOL (**L44**)and 3,3′-CN_2-BINOL (**L45**) ligands (Scheme 32a).[72] A clearly linear correlation is observed, suggesting that a single 3,3′-F_2-BINOL is involved in the stereodetermining step. They further extended the Pd(II)-catalyzed enantioselective methylene C(sp^3)–H alkenylation/aza-Wacker sequence to the construction of γ-lactams bearing contiguous stereogenic centers by employing *gem*-dialkyl amides **106** as the substrates (Scheme 32b).[73]

In 2016, an unprecedented ligand-accelerated Pd(II)-catalyzed enantioselective arylation of unbiased methylene C(sp^3)–H bonds directed by a weakly coordinating monodentate directing group was reported by the Yu group. A novel type of chiral acetyl protected aminoethyl quinoline (APAQ) was developed and **L46** was found to be the best ligand (Scheme 33a).[74] This protocol was compatible with aliphatic amides with various chain lengths and sterically hindered functionalities at the β-, δ- and ε-positions, giving the desired products **115** with good to excellent enantioselectivities.

In 2017, Yu and coworkers achieved the Pd(II)-catalyzed enantioselective desymmetrization of isobutyric amides **116** *via* β-C(sp^3)–H arylation strategy (Scheme 33b).[75] The use of previous developed APAQ ligands gave a nearly racemic arylation product, indicating the difference between the desymmetrization of *gem*-dimethyl and methylene C–H bonds. By the replacement of the quinoline motif with oxazoline, a mono-protected aminomethyl oxazoline ligand (MPAO) **L47** was obtained, which enables the enantioselective β-arylation, -alkenylation, and -alkynylation of isobutyric amides in good yields with high enantiomeric ratios. In addition, the resulting chiral arylation products could be further functionalized by Pd(II)-catalyzed C(sp^3)–H functionalization of the remaining methyl group, providing a new approach to access a myriad of α-chiral carboxylic acids.

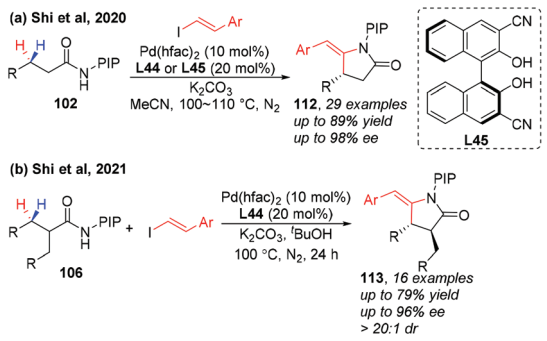


Scheme 33 Pd(II)-Catalyzed enantioselective C(sp^3)–H arylation assisted by weak monodentate directing group.

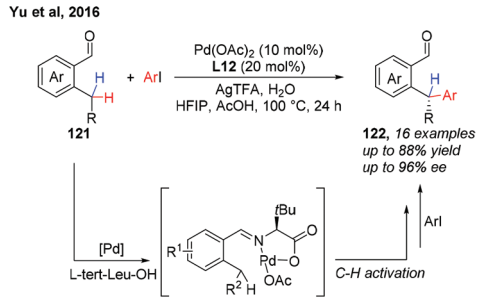
Besides the Pd(II)/Pd(IV) catalytic system, the Yu group employed a Pd(II)/Pd(0) strategy in the Pd(II)/MPAO-catalyzed enantioselective γ-C(sp^3)–H arylation and alkenylation of alkyl amines with aryl and vinyl boronic acids respectively (Scheme 33c).[76] The (*S*,*S*)-MPAO ligand (**L48**) was found compatible in the arylation reactions, giving the corresponding products in high yields and excellent enantioselectivities (up to 98% ee). On the other hand, the use of MPAO (**L49**) with 4-F-benzoyl substituted at the C5 position could significantly improve the yields and the enantioselectivities in C–H alkenylation reaction. A wide range of enantio-enriched alkyl amines were produced with the assistance of this bulky MPAO ligand.

In 2016, Yu and coworkers first broke the limitations of stoichiometric installation and removal of the external directing group in C–H activation and developed a Pd(II)-catalyzed enantioselective methylene C(sp^3)–H arylation of benzaldehydes using commercially available L-*tert*-leu-OH **L12** as the chiral transient directing group (Scheme 34).[77] A wide range of aryl iodides bearing various functional groups and benzaldehydes with various chains were tolerated, affording the arylated products in high yields with excellent enantioselectivities.

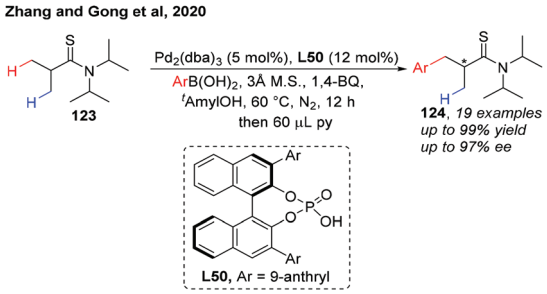
Recently, Gong, Zhang and coworkers developed a Pd-catalyzed enantioselective β-C(sp^3)–H arylation of thioamides with



Scheme 32 PIP-directed Pd-catalyzed enantioselective intramolecular C(sp^3)–H alkenylation/aza-Wacker cyclization.



Scheme 34 Pd(II)-Catalyzed enantioselective C(sp^3)–H arylation of benzaldehydes *via* transient chiral auxiliary strategy.

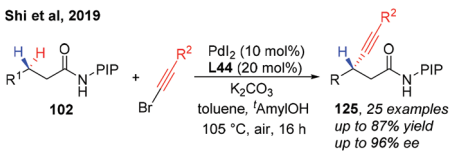


Scheme 35 Pd(II)-Catalyzed enantioselective intermolecular C(sp^3)–H arylation of thioamide.

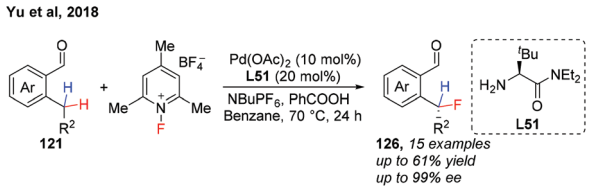
arylboronic acids using chiral CPA **L50** as the ligand (Scheme 35).[78] DFT calculations suggest that a high level of stereocontrol depends on a robust chiral cavity defined by the bulky CPA with a neutral thioamide ligand.

3.1.3 Alkynylation. In 2019, a PIP-directed Pd(II)/3,3′-F_2-BINOL-catalyzed enantioselective alkynylation of unbiased methylene C(sp^3)–H bonds with alkynyl bromides was first developed by the Shi group. In this catalysis, 3,3′-bisubstituted-BINOLs were first identified as a novel type chiral ligand in enantioselective C(sp^3)–H activation (Scheme 36).[69] A broad range of alkynylated aliphatic carboxamides were obtained in good yields with high enantioselectivities. The stereo-determining C–H palladation step might be influenced by multiple ligands based on the positive nonlinear effect.

3.1.4 Fluorination. In 2018, Yu and coworkers reported the Pd(II)-catalysed enantioselective C(sp^3)–H fluorination *via* a chiral transient directing group strategy (Scheme 37).[79] Notably, the use of the bulky amino amide **L35** as TDG not only controls the stereochemistry of the C–H cleavage step but



Scheme 36 Pd(II)-Catalyzed enantioselective methylene C(sp^3)–H alkynylation directed by PIP auxiliary.

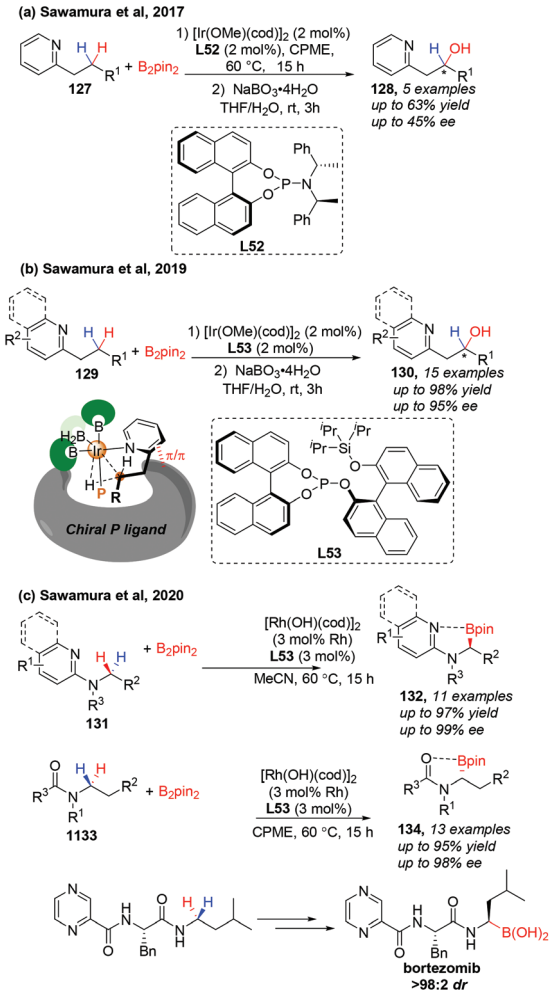


Scheme 37 Pd(II)-Catalyzed enantioselective C(sp^3)–H fluorination.

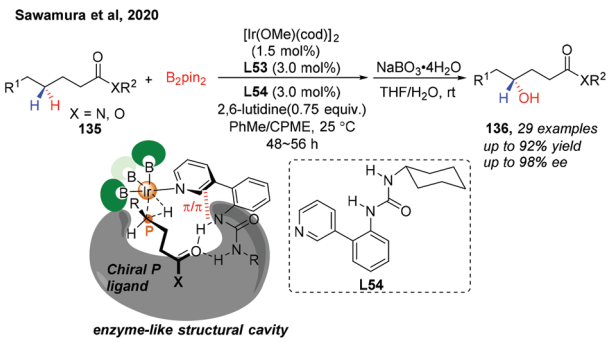
also promotes the selective C(sp^3)–F reductive elimination over the C(sp^3)–O reductive elimination. The fluorinated products were obtained in good yields with high enantioselectivities. Moreover, mechanistic investigations revealed that the C(sp^3)–F formation proceeds *via* an inner-sphere pathway and C(sp^3)–O formation occurs through an SN2-type process.

3.1.5 Borylation. In 2017, Sawamura and coworkers first demonstrated an Ir(I)-catalyzed borylation of the unactivated C(sp^3)–H bond, using chiral phosphoramidite **L52** as the ligand and pyridine as the directing group. Unfortunately, the desired products were formed in low enantioselectivities (Scheme 38a).[80] To improve the enantioselectivity, they designed a new BINOL-based monophosphate **L53** bearing a second BINOL with a TIPS protection group which dramatically improved both the enantioselectivity and reactivity (Scheme 38b).[81] DFT calculations suggest that a newly formed monophosphite-Ir-tris(boryl) complex was considered to be responsible for such higher regio- and enantioselectivity. In this complex, the iridium catalyst not only coordinates with the nitrogen in pyridine which interacts with one of the naphthalene rings of the phosphite *via* π/π stacking but also couples with C–H/π and nonclassical C–H···O hydrogen bonds. In 2020, the same group employed the same ligand in the Rh(I)-catalyzed enantioselective borylation of C(sp^3)–H bonds adjacent to the nitrogen atom for various types of substrates, such as 2-(*N*-alkylamino)heteroaryls and *N*-alkanoyl- or aroyl-based secondary or tertiary amides. This protocol has also been used in the asymmetric synthesis of the antitumor drug molecule bortezomib (Scheme 38c).[82]

Based on their previous investigations, the Sawamura group made a significant breakthrough by the development of an Ir-catalyzed enantioselective remote C(sp^3)–H borylation of aliphatic amides and esters (Scheme 39).[83] In this catalysis, an enzyme-like structural cavity was formed by the catalyst components including the iridium catalyst, the chiral monophosphite ligand (**L54**), an achiral urea–pyridine receptor ligand, and pinacolatoboryl groups. With this enzyme-like structural cavity, the amide substrates are bound not only through the hydrogen bonding of N–H in the urea–pyridine receptor ligand with the carbonyl group but also through other noncovalent interactions with the inner surface of the cavity, such as the π/π interaction between pyridine and one of the naphthalene rings of the phosphite ligand. This unique catalytic structure enables the enantioselective desymmetric γ-methylene C(sp^3)–H borylation of aliphatic carboxylic amides and esters. Control experiments were also conducted, indicating that the urea–pyr-



Scheme 38 Ir(I)-Catalyzed enantioselective C(sp^3)–H borylation using the chiral phosphoramidite ligands.

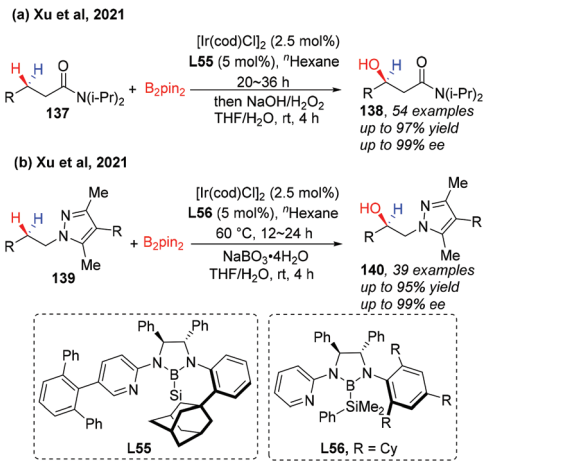


Scheme 39 Ir(I)-Catalyzed enantioselective remote C(sp^3)–H borylation of aliphatic amides and esters.

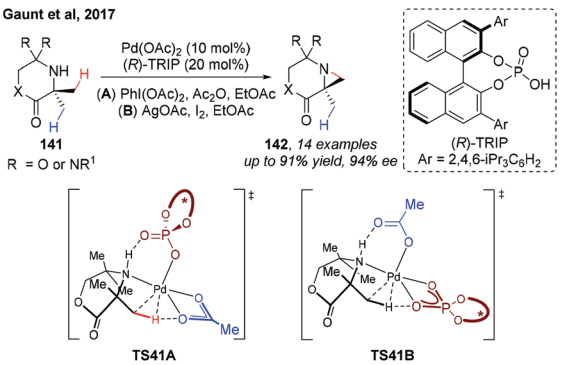
idine receptor ligand is necessary for the C–B bond formation and increasing the loading of this ligand causes a dramatic drop in yield and enantioselectivity.

The Xu group developed a series of chiral bidentate boryl ligands for Ir(I)-catalyzed enantioselective C–H borylation. In 2021, they successfully applied this type of ligand in the carbonyl-directed enantioselective borylation of unbiased methylene C(sp^3)–H bond of acyclic amides (Scheme 40a).[84] A variety of functional groups were well tolerated, affording the borylated amides in good to excellent enantioselectivities. Very recently, the Xu group reported a pyrazole-directed Ir(I)-catalyzed enantioselective β-borylation of unbiased methylene C(sp^3)–H bonds (Scheme 40b).[85] Notably, the high regio- and enantioselectivity strongly depended on the choice of the chiral bidentate boryl ligand, iridium precursor, and pyrazole directing group. Moreover, this pyrazole directing group could be readily elaborated into chiral vicinal diamine derivative *via* ozonolysis.

3.1.6 Amination. In 2017, Gaunt and coworkers reported a Pd(II)-catalyzed enantioselective intramolecular C(sp^3)–H amination of morpholinones and piperazinones using BINOL-phosphoric acid (*R*)-TRIP as the chiral ligand, giving the corresponding chiral aziridines **142** in high yields with good enantioselectivities (Scheme 41).[86a] Based on the experimental studies, they rationalized that one acetate and one TRIP ligand were involved in the enantioselective C–H amination. Two



Scheme 40 Ir(I)-Catalyzed enantioselective unbiased methylene C(sp^3)–H borylation.



Scheme 41 Pd(II)/(*R*)-TRIP-catalyzed enantioselective intramolecular C(sp^3)–H amination.

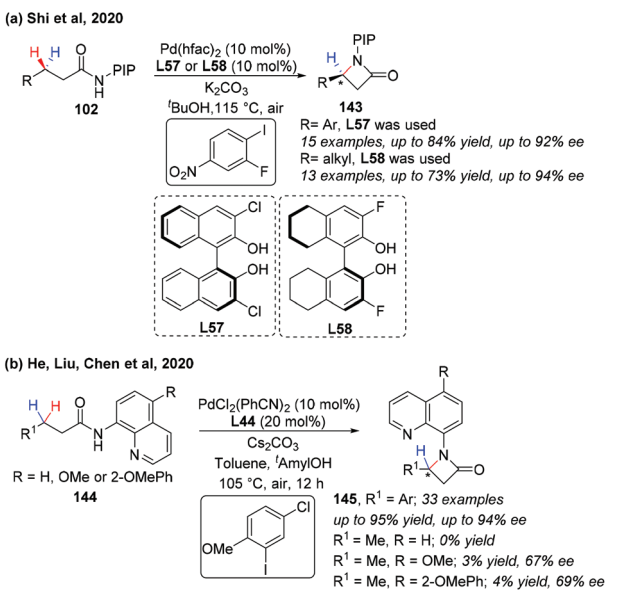
possible modes of C–H cleavage have been proposed by Gaunt and coworkers. In **TS41A**, the hydrogen-bonding interaction between the phosphate ligand and the NH created a rigid transition state for the enantio-determining C–H cleavage *via* a concerted metalation–deprotonation (CMD) pathway using the acetate group. In the other transition state, **TS41B**, hydrogen bonding between the acetate group and amine was involved and the enantio-determining C–H cleavage was assisted by the chiral phosphate ligand. In later computational studies by Zhang, the former was preferred in consideration of the difference in Brønsted basicity between the more basic acetate and the less basic phosphate.[86b]

Inspired by the success of the combination of PIP directing group with Pd(II)/3,3′-disubstituted BINOL catalysis in enantioselective unbiased methylene C(sp^3)–H activation/C–C coupling reactions, the Shi group further developed the synthesis of chiral β-lactams *via* Pd(II)-catalyzed intramolecular enantioselective unbiased methylene C(sp^3)–H amidation in 2020 (Scheme 42a).[87] In the presence of 2-fluoro-1-iodo-4-nitrobenzene as the oxidant, both the benzylic and unbiased C(sp^3)–H bonds were compatible when 3,3′-chlorinated-BINOL **L57** and 3,3′-fluorinated-H_8-BINOL **L58** were used as ligands respectively. The electron-deficient 2-fluoro-1-iodo-4-nitrobenzene enabled the desired C–N reductive elimination over the undesired C–C reductive elimination.

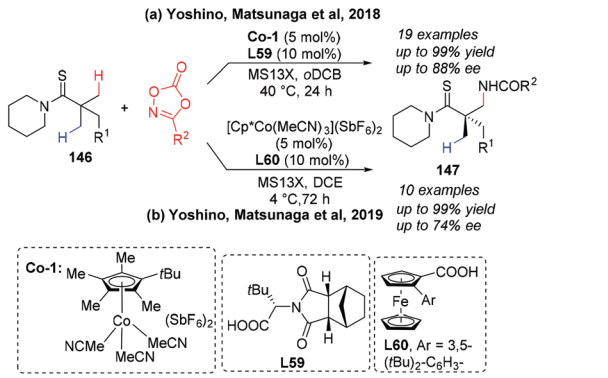
3,3′-F_2-BINOL **L44** has also been applied in 8-aminoquinoline-directed, Pd(II)-catalyzed enantioselective benzylic methylene C(sp^3)–H amidation by He, Liu, Chen and coworkers (Scheme 42b).[88] The use of 2-methoxy-5-chlorophenyl iodide as the oxidant was crucial due to its unique steric and electronic effects, which control the competition of C–N and C–C reductive elimination of the Pd(IV) intermediate, giving the desired chiral β-lactams in moderate to high yields with good to high enantioselectivities. However, a significant low reactivity was obtained for the amidation of unbiased methylene C(sp^3)–H bonds under the same reaction conditions (R^1 = Me, R = H, 0% yield; R^1 = Me, R = OMe; 3% yield, 67% ee; R^1 = Me, R = 2-OMePh; 4% yield, 69% ee).

In 2019, the Yoshino and Matsunaga group reported an unprecedented achiral Cp^xCo(III)/CCA-catalyzed enantioselective C(sp^3)–H amidation of thioamides with dioxazolones *via* a CCA-assisted CMD mechanism (Scheme 43a).[89] The sterically more hindered Cp^xCo(III) catalyst **Co-1** could improve the enantioselectivity but slightly decrease the reactivity. H/D scrambling experiments suggested that the C–H cleavage step was irreversible and the chiral carboxylate induced the enantioselectivity during the CMD process. Later, the same group also developed a 2-aryl ferrocene chiral carboxylic acid **L60** for the Co(III)-catalyzed asymmetric C(sp^3)–H amidation of thioamide (Scheme 43b).[90]

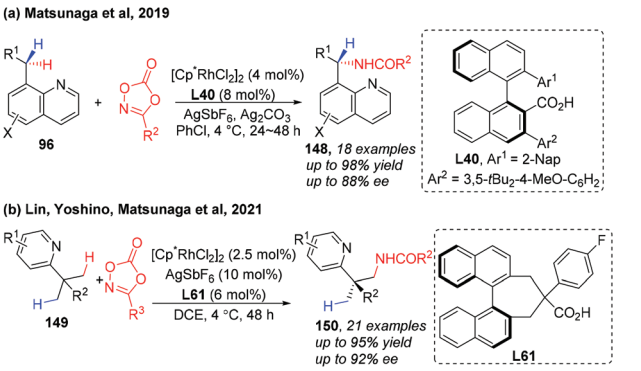
In 2019, Yoshino, Matsunaga and coworkers also described an achiral Cp^xRh(III)/CCA-catalyzed enantioselective methylene C(sp^3)–H amidation of 8-alkylquinolines (Scheme 44a).[64] Essential to the success was the design of a novel binaphthyl-based CCA **L40**. Very recently, a new type of binaphthyl-based pseudo-C_2-symmetric CCA **L61** were developed by the same research group, which shows high reactivity and enantio-



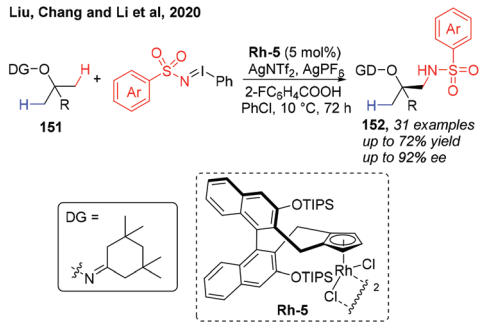
Scheme 42 Pd(II)-Catalyzed enantioselective intramolecular C(sp^3)–H amidation.



Scheme 43 Achiral Cp^xCo(III)/CCA-catalyzed enantioselective C(sp^3)–H amidation of thioamides.



Scheme 44 Cp*Rh(III)-Catalyzed enantioselective C(sp^3)–H amidation.



Scheme 45 Chiral $Cp^xRh(III)$-catalyzed enantioselective $C(sp^3)$–H amidation.

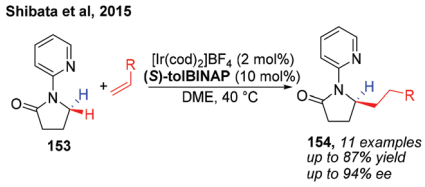
control in $Cp^xRh(III)$-catalyzed enantioselective $C(sp^3)$–H amidation of 2-alkylpyridine derivatives (Scheme 44b).[91]

In 2020, Liu, Chang, Li and coworkers reported the chiral $Cp^xRh(III)$-catalyzed enantioselective desymmetric $C(sp^3)$–H amidation of *gem*-dimethyl groups, providing chiral β-amino alcohols with moderate to good yields with high enantioselectivities (Scheme 45).[92] The steric bulk of the R groups could significantly affect the enantioselectivity as low enantioselectivities were observed when smaller R groups were introduced. In addition, the ring size and steric effects of the oxime directing group also played a crucial role in controlling enantioselectivity.

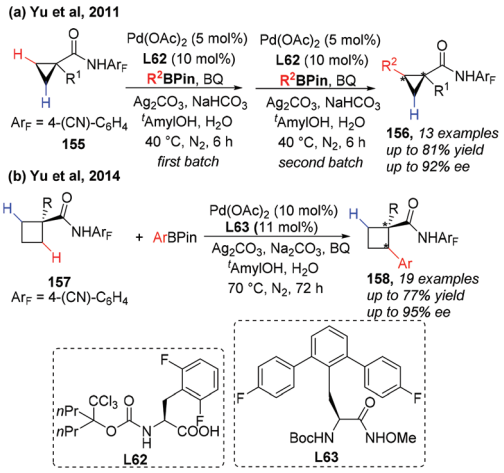
3.2 Desymmetric $C(sp^3)$–H functionalizations of cycloalkanes

3.2.1 Alkylation. After Shibata and coworkers reported the Ir(I)-catalyzed enantioselective $C(sp^3)$–H alkylation of the 2-(alkylamino)pyridines using the (*S*)-tolBINAP as the chiral ligand (Scheme 28a),[60] they further examined the feasibility of this strategy with *N*-(2-pyridyl)-γ-butyrolactams (Scheme 46).[93] The desired chiral alkylated products were obtained in good yields and enantioselectivities and could be further transferred to 4-substituted-β-amino acid derivatives. Besides, this protocol could also be used as a key step for the synthesis of Pyrrolam A.

3.2.2 Arylation. In 2011, Yu and coworkers reported the first Pd(II)-catalyzed enantioselective $C(sp^3)$–H activation of cyclopropanes directed by a weakly coordinating *N*-arylamide directing group using MPAA **L62** as the ligand (Scheme 47a).[94] The reagents (excluding the substrate) were added in two batches and various aryl-, vinyl-, and alkylboron reagents can be tolerated, affording the desired chiral products **156** in moderate to good yields with good to high enantioselectivities. The



Scheme 46 Ir(I)-Catalyzed enantioselective $C(sp^3)$–H alkylation.

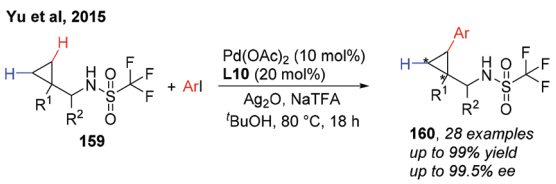


Scheme 47 Pd(II)-Catalyzed enantioselective $C(sp^3)$–H arylation of cyclopropanes and cyclobutanes.

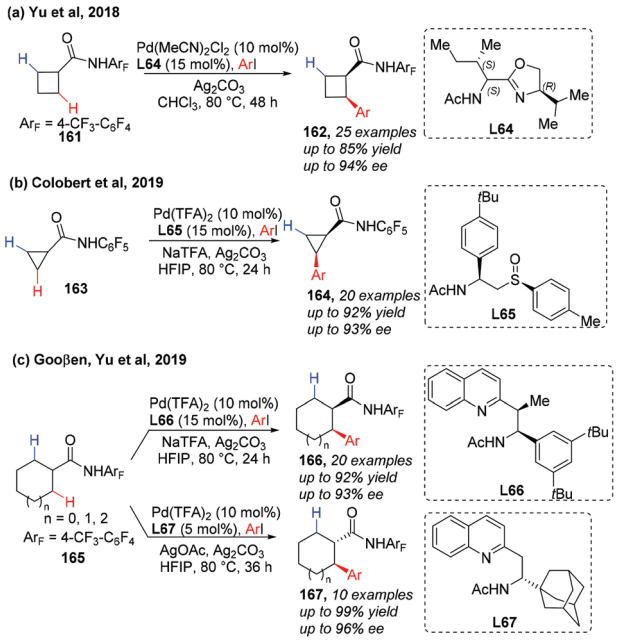
investigation regarding the modified MPAA ligands indicated that the CCl_3 moiety served as a sterically bulky group and tuned the electronic properties of the nitrogen atom through its electron-withdrawing character. In 2014, Yu and coworkers designed a new type of mono-*N*-protected α-amino-*O*-methylhydroxamic acid ligands for Pd(II)-catalyzed enantioselective desymmetric $C(sp^3)$–H arylation of cyclobutanecarboxylic acid derivatives (Scheme 47b).[95] Various cyclobutyl carboxamides bearing an α-quaternary carbon center were compatible with this protocol, giving the desired products in good yields with high enantioselectivities. Unfortunately, poor yields and enantioselectivities were observed for substrates containing α-hydrogen atom and prochiral acyclic unactivated methyl $C(sp^3)$–H bonds.

In 2015, Yu and coworkers reported a Pd(II)-catalyzed enantioselective $C(sp^3)$–H arylation of cyclopropylmethylamines **156** with aryl iodides using Boc-L-Val-OH **L10** as the ligand *via* a Pd(II)/Pd(IV) catalytic cycle (Scheme 48).[96] Chiral *cis*-aryl-products were obtained in excellent yields (up to 99%) and enantiomeric excesses (up to 99.5% ee). A Pd(II)/Pd(0) catalytic cycle was ruled out due to the lack of a trace reaction in the absence of a silver salt. Notably, the silver salt not only promotes the oxidative addition of Ar–I but also facilitates the reductive elimination by interacting with the iodide.

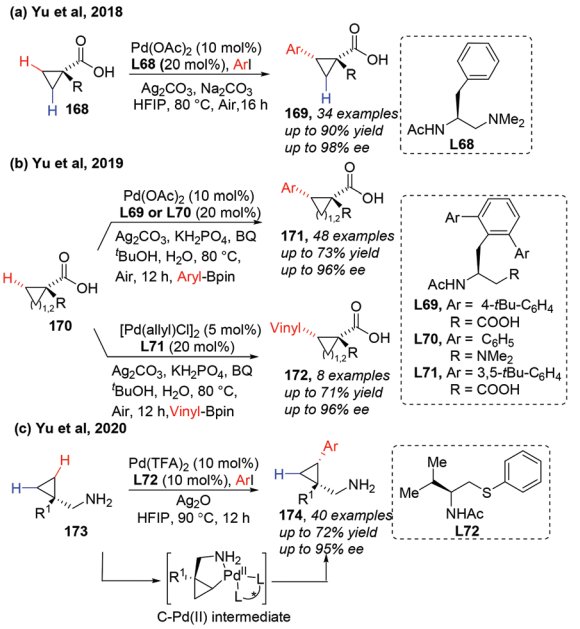
In 2018, Yu and coworkers further achieved the Pd(II)-catalyzed enantioselective $C(sp^3)$–H arylation of cyclobutyl car-



Scheme 48 Pd(II)-Catalyzed enantioselective $C(sp^3)$–H arylation of cyclopropylmethylamines.



Scheme 49 Pd(II)-Catalyzed enantioselective intermolecular C(sp^3)–H arylation of cycloalkane carboxamides.



Scheme 50 Pd(II)-Catalyzed enantioselective C(sp^3)–H functionalization.

boxylic amides (Scheme 49a).[97] Utilizing MPAO **L64** as the chiral ligand, an array of substituted cyclobutanes containing α-hydrogen atoms were well tolerated and their corresponding chiral arylated derivatives were afforded in moderate to good yields with excellent enantioselectivities.

In 2019, the Colobert group reported a Pd(II)-catalyzed enantioselective C(sp^3)–H arylation of cyclopropyl carboxylic amides using easily accessible *N*-acetyl aminosulfoxide **L65** as an efficient chiral ligand (Scheme 49b).[98] Mechanistic studies revealed that noncovalent interactions between the chiral complex and the substrate were crucial for enantiocontrol. Moreover, this catalysis could also be applied to the enantioselective C(sp^3)–H alkynylation reaction.

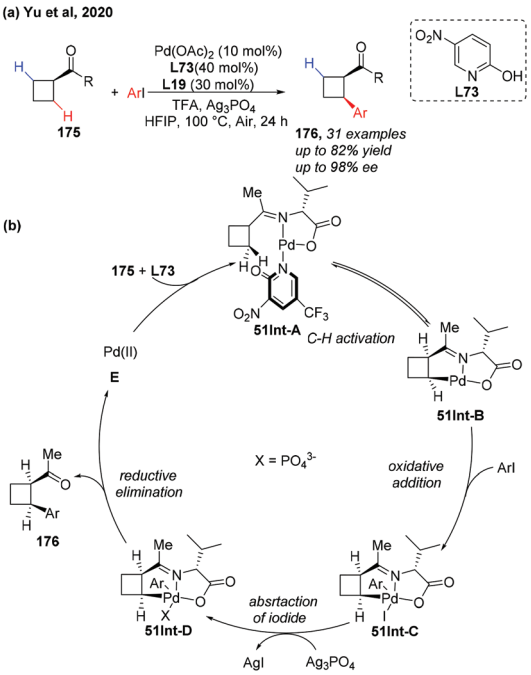
Gooßen, Yu and coworkers demonstrated a Pd(II)-catalyzed enantioselective and diastereoselective C(sp^3)–H arylation of cycloalkane carboxamides using APAQ ligands (**L66** and **L67**) (Scheme 49c).[99] Remarkably, the arylation of five- and seven-member cycloalkanes were also produced in good yields with high diastereoselectivities and enantioselectivities.

In 2018, Yu and coworkers developed a Pd(II)-catalyzed enantioselective C(sp^3)–H arylation of cyclopropanecarboxylic acids with aryl iodides using free carboxylic acid as the directing group (Scheme 50a).[100] The use of monoprotected aminoethyl amine (MPAAM) **L68** as the chiral ligand gave chiral arylated cyclopropanecarboxylic acids in high yields and enantioselectivities. Soon after, a Pd-catalyzed enantioselective C(sp^3)–H activation/cross-coupling reaction of cyclopropane/cyclobutane carboxylic acid with organoborons was reported by the same group *via* the Pd(II)/Pd(0) catalytic cycle (Scheme 50b).[101] The use of 2,6-di-substituted phenylalanine-derived ligands (**L69–L71**) was crucial for high enantiocontrol. The arylation reaction proceeded in good yields and enantioselectivities when **L69** and **L70** were used as chiral ligands while the use of **L71** as the ligand enabled high enantioselective C(sp^3)–H vinylation.

In 2020, the use of free amine as the directing group on Pd-catalyzed enantioselective C(sp^3)–H functionalization was developed by Yu and coworkers (Scheme 50c).[102] The use of chiral bidentate thioether ligand **L72** resulted in the formation of a versatile chiral C–Pd(II) intermediate *via* enantioselective C–H activation. Such an intermediate can not only react with (hetero)aryl iodides *via* the Pd(II)/Pd(IV) catalytic cycle to deliver chiral γ-(hetero)aryl cyclopropylmethylamines but also can give the carbonylation and olefination products *via* a Pd(II)/Pd(0) pathway.

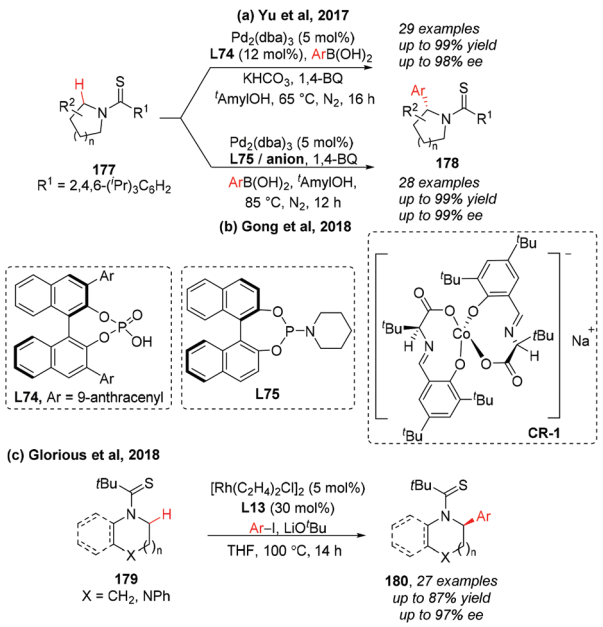
Recently, Yu and coworkers developed a Pd(II)-catalyzed enantioselective C(sp^3)–H arylation of cyclobutyl ketones using L-valine **L19** as a chiral transient directing group (Scheme 51a).[103] The use of electron-deficient 2-pyridone ligand **L73** and Ag_3PO_4 was key to high enantioselectivity and yield. A plausible reaction mechanism is proposed in Scheme 51b. The cyclometalated Pd(II)-complexes **51Int-B** are initially generated from **51Int-A** *via* pyridone ligand accelerated C–H bond cleavage. Then followed by oxidative addition with aryl iodide resulted in the formation of Pd(IV) complexes **51Int-C**, which underwent ligand exchange to give intermediate **51Int-D** in the presence of Ag_3PO_4. The subsequent reductive elimination and hydrolysis of **51Int-D** led to the formation of the desired arylation product **173** and Pd(II) species.

Saturated aza-heterocycles are privileged building blocks that widely exist in bioactive molecules. In 2017, Yu and coworkers reported a Pd(II)-catalyzed enantioselective α-C(sp^3)–H arylation of thioamides with arylboronic acids using chiral



Scheme 51 Pd(II)-Catalyzed enantioselective intermolecular C(sp^3)–H arylation of cyclobutyl ketones.

phosphoric acids (CPA) **L74** as the chiral ligand (Scheme 52a).[104] The system is highly enantioselective and regioselective for diverse aza-heterocycles, such as azetidines, pyrrolidines, piperidines and azepanes. Later, Gong and co-workers reported an unprecedent Pd(II)-catalyzed asymmetric thioamide-directed α-C(sp^3)–H arylation *via* a hybrid chiral pal-



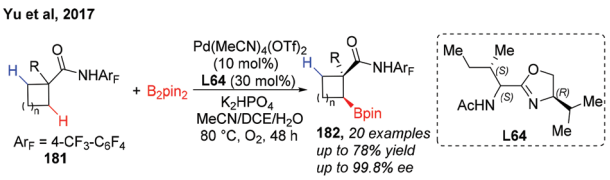
Scheme 52 Enantioselective C(sp^3)–H arylation of saturated aza-heterocycles directed by thioamides.

ladium catalyst consisting of a chiral phosphoramidite ligand **L75** and a chiral Co(III) anion (**CR1**) (Scheme 52b).[105] Significant synergy between the chiral ligand and the chiral anion is crucial for high enantiocontrol.

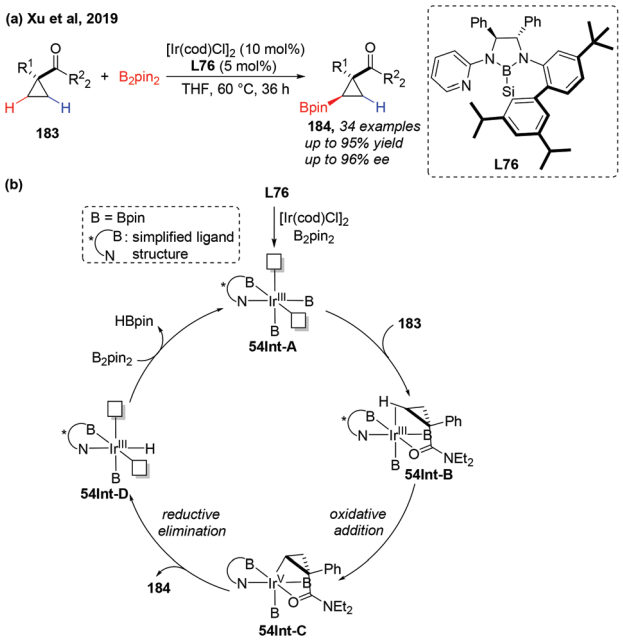
In 2018, the Glorious group reported the first enantioselective Rh(I)-catalyzed enantioselective C(sp^3)–H arylation of various saturated aza-heterocycles with aryl iodides (Scheme 52c).[106] The use of chiral monodentate phosphonite **L13** as the chiral ligand and thioamide as the directing group enabled the formation of a variety of important enantio-enriched heterocycles, including α-*N*-arylated tetrahydroquinolines and piperazines, in high yields and enantioselectivities.

3.2.3 Borylation. In 2017, Yu and coworkers reported a Pd(II)-catalyzed enantioselective C(sp^3)–H borylation directed by weakly coordinating carboxylic amide using APAO **L64** (Scheme 53).[107] This Pd(II)/Pd(0) system is compatible with substrates containing α-tertiary as well as α-quaternary carbon centres.

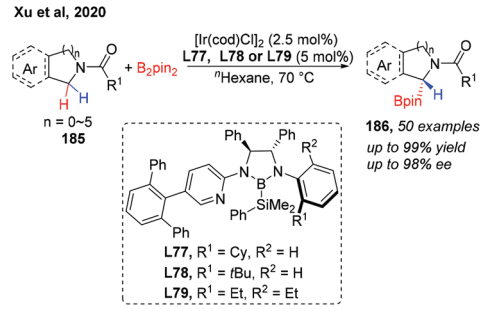
In 2019, Xu and coworkers reported the application of their newly designed ligands in an Ir-catalyzed enantioselective desymmetric C(sp^3)–H borylation of cyclopropanes (Scheme 54a).[108] A possible reaction pathway for this boryla-



Scheme 53 Pd(II)-Catalyzed enantioselective C(sp^3)–H borylation.



Scheme 54 Ir(I)-Catalyzed enantioselective C(sp^3)–H borylation.



Scheme 55 Ir(I)-Catalyzed enantioselective C(sp^3)–H borylation of azacycles.

tion is depicted in Scheme 54b. The reaction is initiated by the reaction of **L76** with $[Ir(cod)Cl]_2$ and B_2pin_2 to give a chiral trisboryl Ir(III) complex **54Int-A**, which is then coordinated with the substrate to generate **54Int-B**. Thereafter oxidative cleavage of C(sp^3)–H bond results in Ir(V) complex **54Int-C**, which undergoes reductive elimination to furnish the borylated product. The active catalyst is regenerated in the presence of B_2pin_2 to close the catalytic cycle.

Soon after, the same group further successfully applied this enantioselective borylation strategy to the C(sp^3)–H activation of cyclic azacycles using the modified chiral bidentate boryl ligands (Scheme 55).[109] A variety of bioactive azacycles were tolerated in this catalysis, yielding the corresponding borylation products with high enantioselectivities. The synthetic utility of this catalysis was also shown in the further derivatizations, gram scale synthesis and the total synthesis of (+)-calycotomine.

4. Conclusions

Over the past decade, coordination-assisted transition-metal-catalyzed enantioselective desymmetric C–H functionalization has demonstrated its potential in the synthesis of enantio-enriched molecules bearing point, axial and planner chirality. The nature of this strategy overcomes the limitation of traditional enantioselective desymmetrization reactions caused by the synthesis and utilizing of preformed multifunctional symmetric substrates and increases the practicality in synthetic chemistry. Despite the significant achievements that have been made, several challenges remain to be tackled. First, the use of abundant and inexpensive 3d-transition-metals in enantioselective desymmetric C–H activation is still in its infancy even though increasing attention has been devoted to this area in terms of its environmental friendliness and economically attractive properties. Second, although the formation of carbon–carbon bonds *via* transition-metal-catalyzed enantioselective C–H functionalization has received ample success, the formation of carbon–heteroatom bonds is still underdeveloped. Third, unactivated remote C(sp^3)–H desymmetrization is still a fundamental challenge owing to the extra entropic penalty for the formation of larger-member metallacycles. Finally, several drawbacks, such as the use of high catalyst loading and harsh reaction conditions, have greatly limited the application in the pharmaceutical industry and total synthesis of natural products. Therefore, the development of novel chiral ligands and new innovative strategies is urgently demanded to stimulate further development of this cutting-edge field.

Conflicts of interest

There are no conflicts to declare.

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