

Chemical Science

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: K. Yang, M. Song, H. Liu and H. Ge, *Chem. Sci.*, 2020, DOI: 10.1039/D0SC03052J.



This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

ARTICLE

Palladium-catalyzed direct asymmetric C–H bond functionalization enabled by the directing group strategy

Ke Yang,^a Mengjie Song,^a Hao Liu^b and Haibo Ge^{*b}Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

In the past decade, the selective C–C and C–heteroatom bond construction through the palladium-catalyzed direct C–H bond functionalization has been extensively studied by employing a variety of directing groups. Within this category, direct asymmetric C(sp²)–H and C(sp³)–H activation for the construction of highly enantiomerically enriched skeletons still progressed at a slow pace. This minireview briefly introduces the major advances in the field for the palladium-catalyzed direct asymmetric C–H bond functionalization via the directing group strategy.

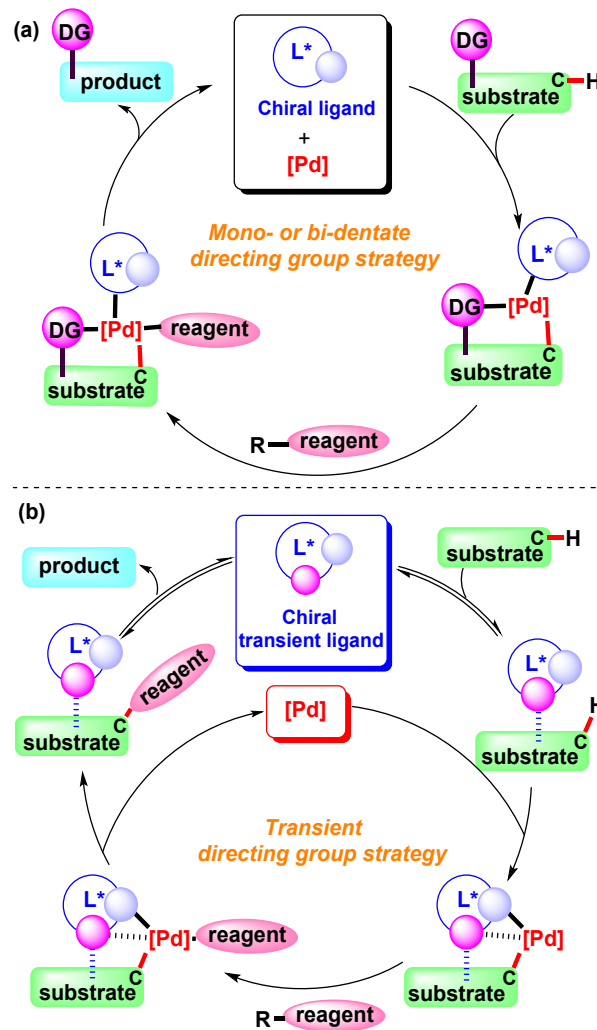
1. Introduction

Transition metal-catalyzed C–H bond functionalization is one of most efficient approaches for the selective C–C and C–heteroatom bond construction in organic synthesis.¹ Among various transition metal catalysts, palladium species have been recognized as the most important ones in the direct C–H bond functionalization reactions.²

In the past decade, palladium-catalyzed selective C(sp²)–H and C(sp³)–H bond functionalization has been well demonstrated by covalently attaching a directing group to a substrate.³ In spite of being a powerful approach, additional reaction steps are required for the pre-installation and subsequent removal of the directing group, which decreases the overall efficiency of the process. To overcome this drawback, the transient directing group strategy has been recently developed and successfully applied in the field of C–H bond functionalization. In this process, an external ligand is added to the reaction system to bind to the substrate in a reversible mode and subsequently coordinate to the metal centre.⁴ As a result, no additional synthetic steps are needed for pre-functionalization of the substrate and removal of the directing group, which greatly improves the compatibility and efficiency of the reaction.

Meanwhile, direct asymmetric C–H bond functionalization has also attracted considerable attention due to its promise as the most efficient method to access highly enantiomerically enriched skeletons,^{5–11} and significant progress has been made in the directing group strategy enabled palladium catalysis. Remarkably, the asymmetric version of the process has also been achieved with the assistance of a catalytic amount of chiral ligand or chiral directing group. It was demonstrated by Yu and co-workers in 2008 that a catalytic amount of mono-*N*-protected amino acids (MPAAs) could serve as chiral ligands for the Pd-catalyzed asymmetric C–H bond functionalization.⁶ Furthermore, a breakthrough on the transient directing group strategy has been achieved in the same

group⁷ using *L*-tert-Leucine as a transient ligand for the Pd-catalyzed enantioselective benzylic C(sp³)–H functionalization.



Scheme 1. Concept of palladium-catalyzed direct asymmetric C–H bond functionalization enabled by the directing group strategy

^a Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, School of Petrochemical Engineering, Changzhou University, Changzhou, Jiangsu 213164, China

^b Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409, USA
E-mail: haibo.ge@ttu.edu



Recently, several related reviews or accounts on transition metal-catalyzed direct asymmetric C–H functionalization have been reported^{5a, 8–11}. The Ackermann's minireview summarized the remarkable recent advances in direct asymmetric C–H functionalization catalyzed by earth-abundant 3d transition metals.^{5a} The Yu's account highlighted their development of bifunctional MPAA ligands for the diverse C–H bond functionalization reactions,^{8a} and the review mainly illustrated the recent literatures about transition-metal (Pd-, Ir- and Rh-) catalyzed asymmetric C(sp³)–H bond functionalization by using a specific chiral ligand and scaffold.^{8b} The You group summarized the recent progress for the construction of planar chiral ferrocenes through transition-metal (Cu-, Pd-, Ir-, Rh-, Au- and Pt-) catalyzed asymmetric C–H bond functionalization.⁹ The Shi's review provided an overview principally for the synthesis of axially chiral biaryls.¹⁰ The Cramer's review focused mainly on the Rh- and Ir-catalyzed asymmetric transformations.¹¹

In this mini-review, we will introduce and discuss the significant progress made in the field of palladium-catalyzed asymmetric C–H functionalization using a monodentate, bidentate, or transient directing group (Scheme 1). We will also provide informative summarization of the directing group strategy and outlook of transient directing groups in the transition metal-catalyzed asymmetric C–H bond functionalization.

2. Monodentate directing group-enabled asymmetric C–H functionalization

Monodentate directing groups, such as amide, ester, carboxylic acid, ketone, heterocyclic, amine, imine, hydroxyl groups and so on, have been well studied for the Pd-catalyzed C–H functionalization reactions. Moreover, sulfur and phosphorus-containing monodentate directing groups have also been developed. Despite these great achievements, realization of Pd-catalyzed asymmetric C–H functionalization in the presence of a catalytic amount of chiral ligand is still a challenging process.³

Asymmetric desymmetrization is a unique and important asymmetric synthesis strategy in organic chemistry, and its targets are structurally symmetric compounds with prochirality or *meso*-substrates.¹² In 2005, the Yu group utilized a chiral *tert*-leucine derived oxazoline directing group to achieve the Pd(II)-catalyzed diastereoselective iodination and acetoxylation of C(sp³)–H bonds.^{13a–b} Encouraged by these important work, an efficient Pd(II)-catalyzed asymmetric desymmetrization of prochiral diaryl-2-pyridylmethanes with alkyl boronic acids was then established by employing MPAA ligands (Scheme 2a).⁶ After evaluating various commercially available chiral carboxylates and chiral phosphates, (–)-Men-Leu-OH (**L1**) was proved as the optimal ligand and provided the desired products in excellent yields and enantioselectivities.

A plausible catalytic cycle involving the Pd(II)/Pd(0) catalysis was proposed (Scheme 2b). The selective C–H bond cleavage of diaryl-2-pyridylmethane with a Pd(II) catalyst in the presence of (–)-Men-Leu-OH generates the corresponding cyclic Pd(II) intermediate **A**. Next, transmetalation between this intermediate and an alkyl boronic acid provides the intermediate **B**. Finally, the desired chiral product is formed through a reductive elimination process along with a Pd(0) complex.

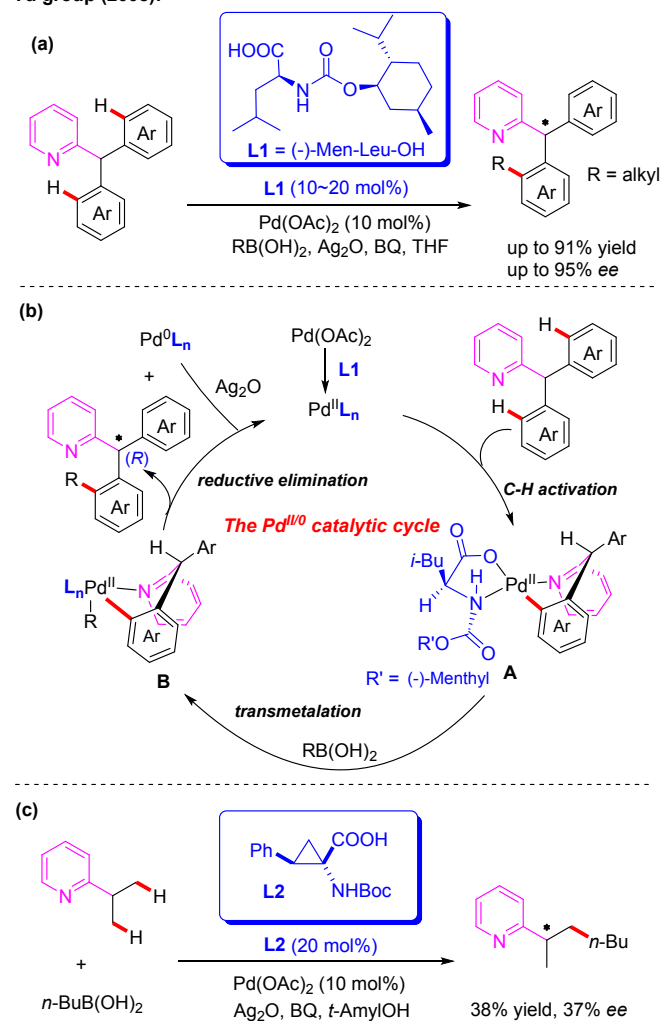
For structure of the proposed cyclic Pd(II) intermediate **A**, the *i*-Bu group is above the palladium plane, and the (–)-menthyloxycarbonyl group is on the palladium plane. Due to the conformational requirements, the non-participating aryl group prefers a less space-crowded axial position, which ultimately results in a (*R*)-configured alkyl product.

In this reaction, BQ was found to be very critical for both the C–H bond activation and reductive elimination. The silver salt was proposed to act

as an oxidizing reagent in the process to re-oxidize the resulted Pd(0) complex to the corresponding Pd(II) complex. Notably, a very recent DFT theoretical calculation study indicates that an important molecular interaction between the Pd(II) catalyst and the silver salt additive may exist in the critical transition states of aryl C(sp²)–H bond activation process. Silver salt is likely to manifest in the form of a Pd–Ag heterobimetallic species in the whole catalytic cycle, not just as a terminal oxidant.^{13c} Moreover, in the presence of a cyclopropane amino acid ligand **L2**, the enantioselective C(sp³)–H alkylation of 2-isopropylpyridine with butyl boronic acid was also developed and desired product was obtained in 38% yield and 37% ee (Scheme 2c).

Carboxylic acids, as cheap and readily available reagents, are widely used in organic chemistry.^{13d} In 2010, the Yu group demonstrated a desymmetric C–H olefination of diarylacetic acids using Boc-L-isoleucine (**L3**) as a chiral ligand (Scheme 3a).¹⁴ In order to obtain high yield and enantioselectivity, the unique combination of sodium diphenylacetate and KHCO₃ is applied in this reaction. Moreover, structure of the (*R*)-configured olefination product was confirmed by the X-ray analysis, which was consistent with the proposed cyclic Pd(II) intermediate (Scheme 3b). These results demonstrated that MPAA ligands could effectively promote stereo induction in the Pd(II)-catalyzed asymmetric C–H bond functionalization.

Yu group (2008):

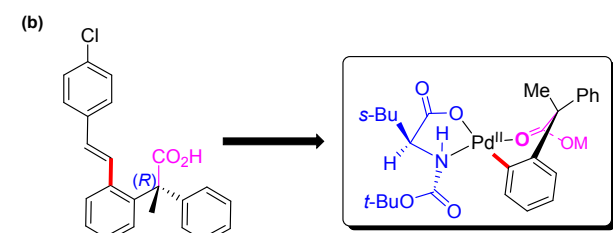
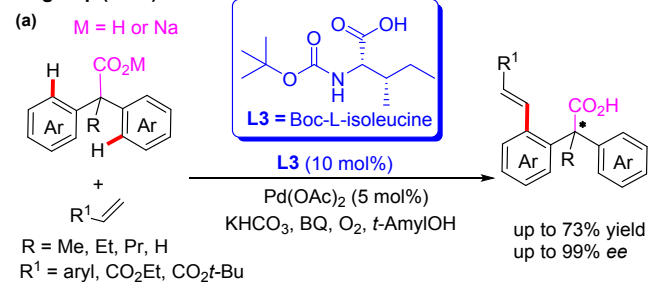


Scheme 2 External MPAA ligands for the Pd(II)-catalyzed C–H asymmetric



desymmetrization of diaryl-2-pyridylmethanes and 2-isopropylpyridine with alkyl boronic acids

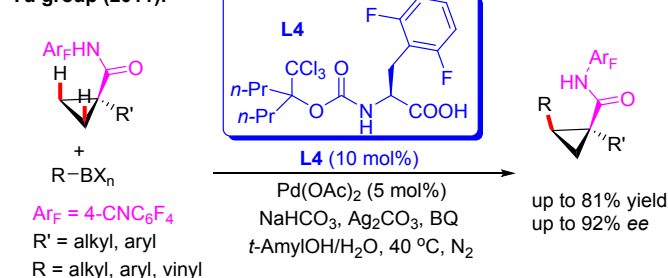
Yu group (2010):



X-ray analysis confirmed

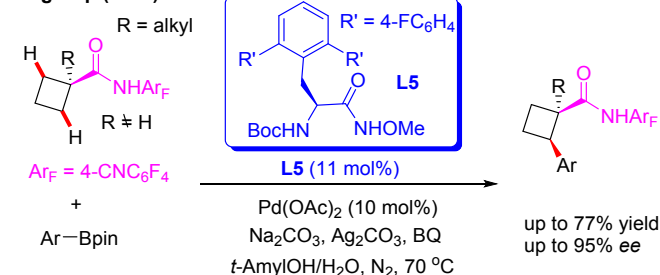
Scheme 3. Pd(II)-catalyzed desymmetric C–H olefination of diphenylacetic acids using Boc-L-isoleucine as a chiral ligand

Yu group (2011):



Scheme 4. Pd(II)-catalyzed asymmetric C–H bond activation of cyclopropane acid derived amides in the presence of a chiral ligand **L4**

Yu group (2014):



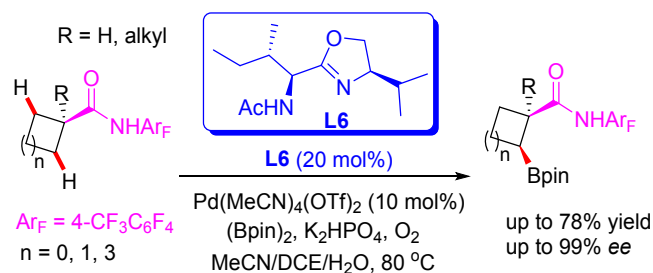
Scheme 5 Pd(II)-catalyzed asymmetric β -C(sp³)-H arylation of cyclobutyl carboxylic acid derived amide with arylboron reagents

In 2011, the Yu group reported the first example of asymmetric C–H bond activation of cyclopropane carboxylic acid derived 4-

cyanotetrafluorophenyl amides in the presence of a novel mono-*N*-protected amino acid ligand **L4** (Scheme 4).¹⁵ A range of organoboron reagents, such as aryl, vinyl, and alkylboron compounds, were used to afford *cis*-substituted chiral products in good to excellent enantioselectivities (up to 81% yield and 99% ee). It was proposed that use of the strongly electron-withdrawing 4-cyanotetrafluorophenyl-substituted amide as a weakly coordinating group could increase the acidity of the N–H bond, enabling deprotonation of substrates under weakly basic conditions, and thus facilitating subsequent C–H bond cleavage with a Pd(II) catalyst. Furthermore, this novel ligand **L4** presents two specific features: (1) the withdrawing trichloromethyl group increases steric size while also adjusting the electronic properties of the nitrogen atom, and (2) the 2,6-difluorophenyl group protects the arene from metalation due to its rigid steric environment.

After a short while, the first example of Pd(II)-catalyzed asymmetric methylene β -C(sp³)-H functionalization of cyclobutane carboxylic acid derived 4-cyanotetrafluorophenyl amides with arylboron reagents was also reported by the Yu group (Scheme 5).¹⁶ In this study, it was found that with MPAAAs as chiral ligands, only low yield and poor ee could be achieved. However, mono *N*-protected α -amino-*O*-methylhydroxamic acid (MPAHA) ligand **L5** afforded high enantioselectivities. The possible reason for the improved performance is presumably due to the much tighter binding of *N*-methoxyamide to the palladium catalyst. However, cyclobutane substrates bearing α -hydrogen atoms only afford the poor yields.

Yu group (2017):



Scheme 6. Pd(II)-catalyzed enantioselective β -C(sp³)-H borylation of carboxylic acid derived amides

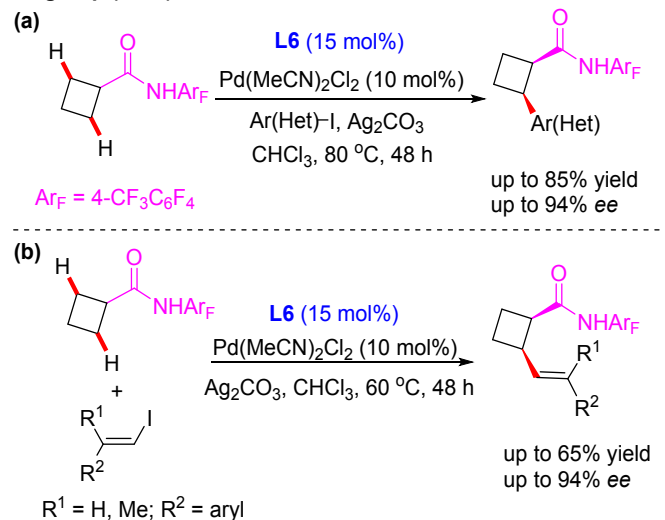
As discussed, asymmetric C(sp³)-H activation reactions could be achieved by employing MPAA or MPAHA ligands. However, the substrate scope was limited in early studies. In 2017, the Yu group reported the first example of Pd(II)-catalyzed enantioselective β -C(sp³)-H borylation of carboxylic acid derived 4-trifluoromethyltetrafluorophenyl amides with (Bpin)₂ in the presence of a chiral acetyl-protected aminomethylloxazoline (APAO) ligand **L6**. In this reaction, various substrates, including cyclopropyl, cyclobutyl and cyclohexyl acid derived amides, were coupled with (Bpin)₂ to afford the desired products in good yields and enantioselectivities (Scheme 6).¹⁷ Notably, this process could provide a complementary approach to achieve enantioselective borylation of amide substrates containing α -tertiary as well as α -quaternary carbon centers.

Subsequently, the same group demonstrated a Pd-catalyzed enantioselective arylation of the cyclobutyl carboxylic acid derived 4-trifluoromethyltetrafluorophenyl amides using the same chiral ligand **L6** (Scheme 7a).¹⁸ Moreover, the first example of enantioselective C(sp³)-H vinylation of cyclobutyl carboxylic acid derived 4-trifluoromethyltetrafluorophenyl amides was developed (Scheme 7b).¹⁸

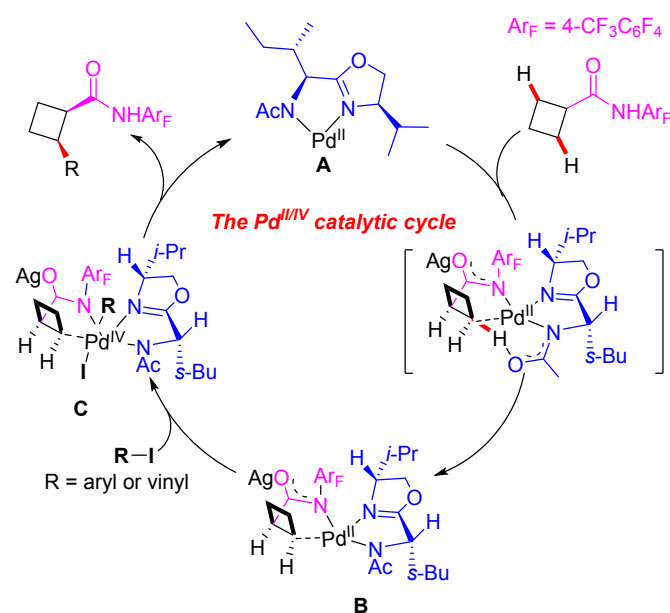


It was also found that only amide substrates containing an α -hydrogen atom were compatible in this process. Notably, compared with MPAA or MPAHA ligands promoted asymmetric C(sp³)-H activation of carboxylic acid derived amides, use of the acidic 4-trifluoromethyltetrafluorophenyl amide as a directing group gave better results in the presence of chiral aminomethyl oxazoline ligands.

Yu group (2018):



Scheme 7. Pd(II)-catalyzed asymmetric arylation and vinylation of the cyclobutyl carboxylic derived amide

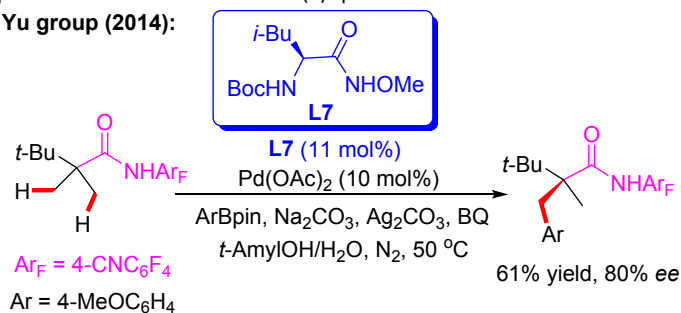


Scheme 8. The proposed mechanism

A plausible catalytic cycle involved a APAO ligand **L6**-enabled a Pd(II)/Pd(IV) catalysis was depicted in Scheme 8, which is different from the previously reported enantioselective Pd(II)/Pd(0) catalysis. First, the pre-coordination of MPAA ligand **L6** with Pd(MeCN)₂Cl₂ provides the chiral Pd(II) species **A**. Subsequent coordination of the substrate to the chiral Pd(II) species **A** followed by a site-selective C-H bond activation

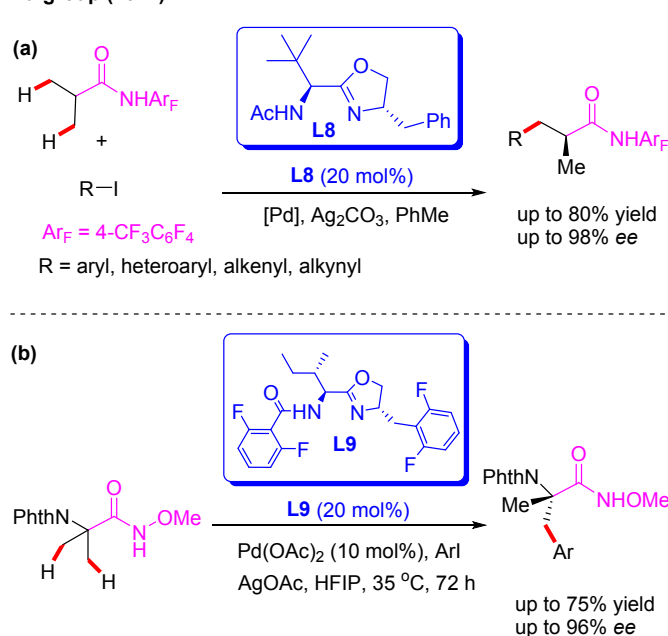
step produces the chiral Pd(II) intermediate **B**. Next, oxidative addition of the intermediate **B** with an aryl or vinyl iodide generates the Pd(IV) complex **C** which undergoes reductive elimination to provide the desired product and release the chiral Pd(II) species **A**.

Yu group (2014):



Scheme 9. The external chiral ligand **L7** for the Pd(II)-catalyzed desymmetric C(sp³)-H activation of prochiral gem-dimethyl groups

Yu group (2017):



Scheme 10. Chiral acetyl- and Bz-protected aminomethyl oxazoline ligands for the Pd(II)-catalyzed asymmetric C-H functionalization

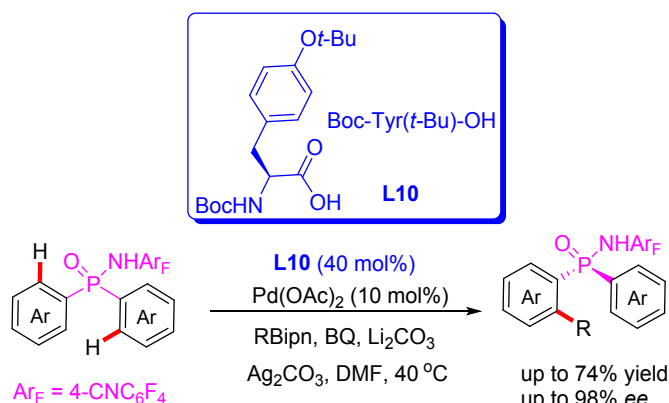
The novel chiral Boc-Leu-NHOMe **L7** was found effective for the desymmetric C(sp³)-H activation of prochiral gem-dimethyl groups. However, only the large sterically hindered substrate (R = *t*-Bu) afforded the desired product in 61% yield and 80% ee (Scheme 9).¹⁶ Later, Yu and co-workers designed a chiral acetyl-protected aminomethyl oxazoline (Ac-PAO) ligand **L8** for the Pd(II)-catalyzed enantioselective β -arylation, alkenylation and alkynylation of isobutyric acid derived 4-trifluoromethyltetrafluorophenyl amides (Scheme 10a). Furthermore, in the presence of a chiral benzoyl-protected aminomethyl oxazoline (Bz-PAO) ligand **L9**, desymmetrization of 2-aminoisobutyric acid derived 4-trifluoromethyltetrafluorophenyl amides has also been achieved (Scheme 10b).¹⁹ The desired α,α -dialkyl α -amino acid derivatives were isolated in good yields and enantioselectivities. Moreover, these derivatives could be used as basic fragments for the construction of peptide-based drugs. The control experiments indicated that



coordination of the chiral center on the oxazoline ring with the substrate is crucial for the above reactions.

P-stereogenic phosphorus derivatives exhibit a prominent chiral induction. However, due to the lack of effective synthetic methods, the application is greatly limited.²⁰ In 2015, the Han group presented the first example of Pd(II)-catalyzed desymmetric C–H arylation of diaryl phosphinamide with boronic ester by using a chiral ligand **L10**. This novel desymmetric strategy afforded a wide array of P-stereogenic phosphinamides in up to 74% yield and 98% *ee*. Furthermore, this process could be used to synthesize various P-stereogenic phosphorus derivatives from P-stereogenic phosphinamides (Scheme 11).²¹

Han group (2015):



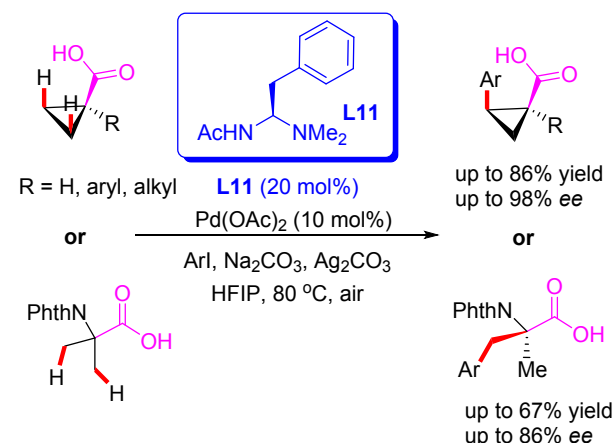
Scheme 11. Pd(II)-catalyzed desymmetric C–H arylation of diaryl phosphinamide with boronic ester

The direct asymmetric desymmetrization of free carboxylic acids provides excellent atom and step economies, because this reaction strategy does not require additional steps to install and remove the directing groups. In 2018, Yu and co-workers designed a novel mono-protected aminoethyl amine (MPAAM) chiral ligand **L11** and achieved the Pd-catalyzed asymmetric arylation of free cyclopropane carboxylic and 2-aminoisobutyric acids (Scheme 12a).²² It was noticed that only arylation through a Pd^{II}/Pd^{IV} catalytic cycle is compatible with this chiral catalyst. Furthermore, this reaction was not compatible with cyclobutane substrates.

Very recently, the same group disclosed a novel method for the asymmetric desymmetrization of free cyclopropane and cyclobutene carboxylic acids with aryl and vinyl organoboron reagents in the presence of either mono-protected amino acid (MPAA) ligand **L12** or mono-protected aminoethyl amine (MPAAM) ligand **L11** through a Pd-catalyzed β -C(sp³)-H activation process (Scheme 12b).²³ Notably, these reactions could also access the desired chiral arylated acids containing α -tertiary and α -quaternary carbon centers. It is proposed that a Pd^{II}/Pd⁰ catalytic cycle might be involved in this process.

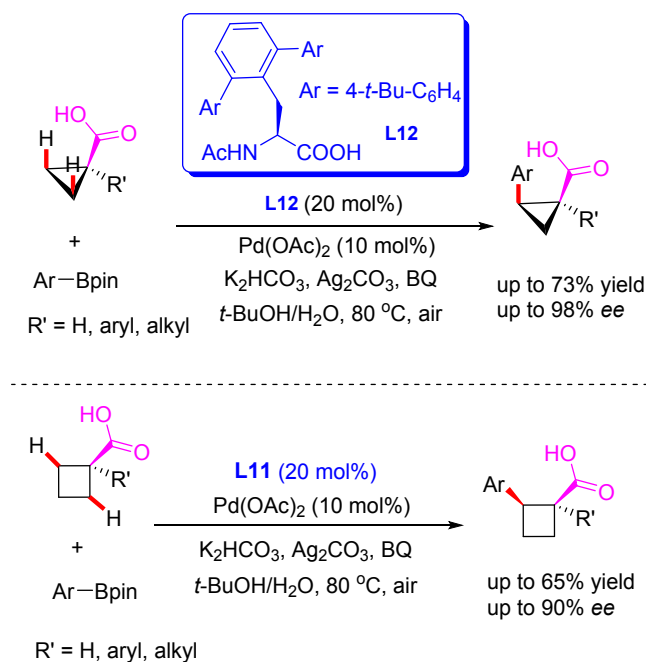
Yu group (2018):

(a): The Pd^{II}/Pd^{IV} catalytic cycle



Yu group (2019):

(b): The Pd^{II}/Pd⁰ catalytic cycle

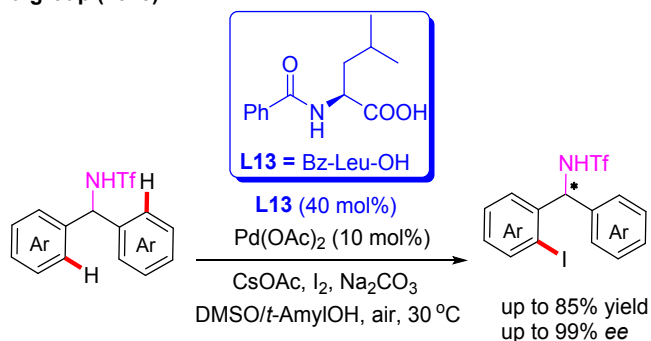


Scheme 12. The direct asymmetric desymmetrization of free carboxylic acids catalyzed by Pd(OAc)₂

Amine derivatives are an important class of synthetically useful compounds in organic chemistry.²⁴ The first example of an asymmetric C–H iodination of Tf-protected diarylmethylamines by using a chiral MPAA ligand **L13** at ambient temperatures was reported by Yu and co-workers in 2013 (Scheme 13).²⁵ In this process, the inexpensive I₂ was used both as the sole oxidant and reaction reagent. In addition, they developed the Pd-catalyzed asymmetric C–H arylation of Tf-protected cyclopropyl methylamines with aryl iodides in the presence of a chiral ligand **L14** (Boc-L-Val-OH) via a Pd^{II}/Pd^{IV} catalytic cycle (Scheme 14). Chiral *cis*-aryl-products were obtained in excellent yields (up to 99%) and enantiomeric excesses (up to 99.5% *ee*).²⁶

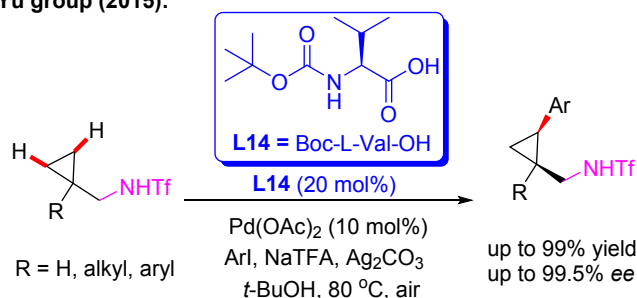


Yu group (2013):



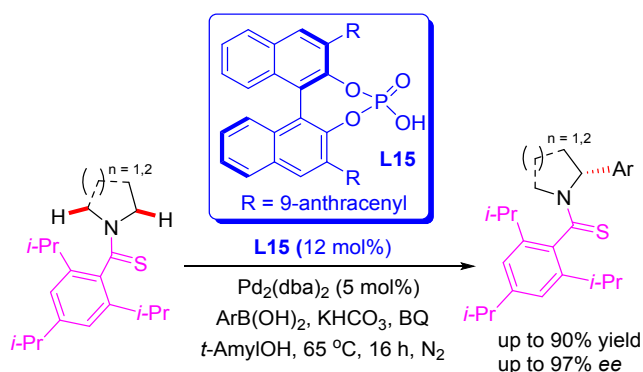
Scheme 13. MPAA-enabled Pd(II)-catalyzed enantioselective C(sp²)-H iodination of Tf-protected diarylmethylamines.

Yu group (2015):



Scheme 14. Pd(II)-catalyzed highly enantioselective C-H arylation of Tf-protected cyclopropylmethylamines

Yu group (2016):

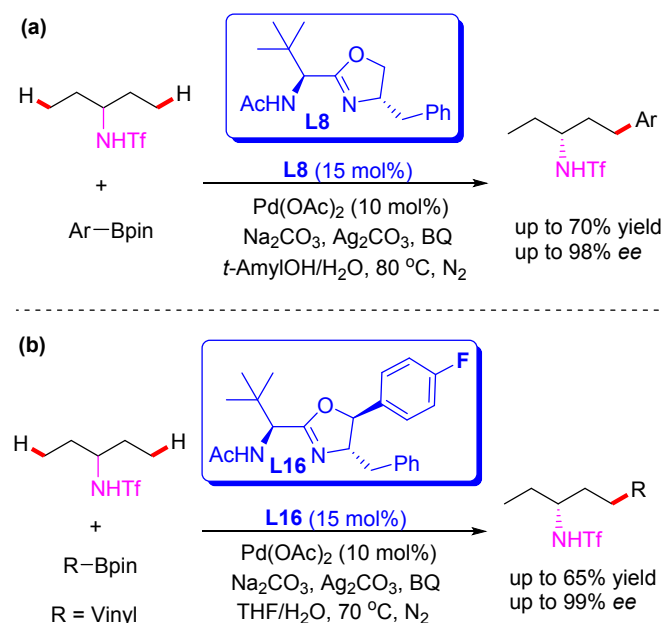


Scheme 15. The asymmetric desymmetrization of amines through a Pd(II)-catalyzed α-C(sp³)-H arylation reaction

In 2016, Yu and co-workers reported the asymmetric desymmetrization of amines through a Pd(II)-catalyzed α-C(sp³)-H arylation process in the presence of a chiral phosphoric acid ligand **L15** (Scheme 15).²⁷ In this reaction, various amines, including ethyl amines, pyrrolidines, azetidines, piperidines, azepanes, indolines, and tetrahydroisoquinolines, were well coupled with aryl boronic acids to construct chiral aryl-amines in excellent yields and enantioselectivities. It is worth noting that chiral phosphoric acids were demonstrated as effective anionic ligands for this asymmetric C-H bond activation. Very recently, the same group reported the asymmetric desymmetrization of

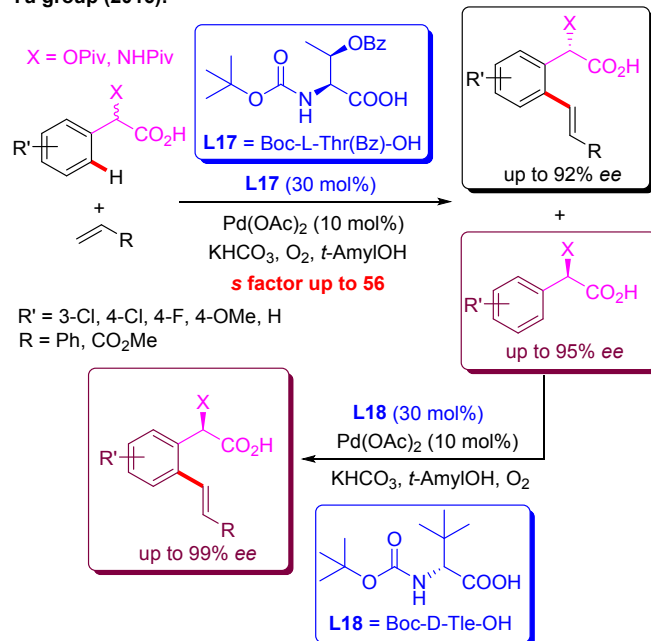
Tf-protected alkyl amines through the Pd(II)-catalyzed enantioselective γ-C(sp³)-H arylation and vinylation by employing the chiral acetyl-protected aminomethyl oxazoline (APAO) ligands **L8** and **L16** (Scheme 16).²⁶

Yu group (2018):



Scheme 16. The asymmetric desymmetrization of Tf-protected alkyl amines through the Pd(II)-catalyzed enantioselective γ-C(sp³)-H arylation and vinylation

Yu group (2016):



Scheme 17. A kinetic resolution strategy for the Pd(II)-catalyzed asymmetric C-H olefination of racemic α-hydroxy and amino phenylacetic acids

While the asymmetric desymmetrization approach is limited to substrates with two prochiral C-H bonds, the kinetic resolution approach

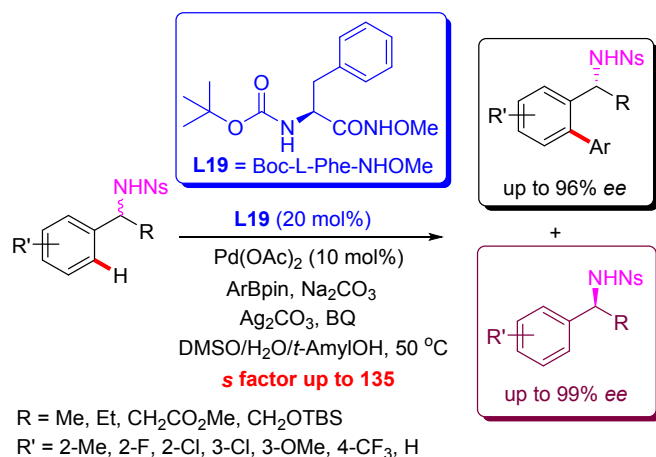


is conceptually different, requiring a different reaction rate between the chiral catalyst and each enantiomer in the racemic mixture.¹¹

In 2016, Yu group developed a kinetic resolution strategy for the Pd(II)-catalyzed asymmetric C–H olefination of racemic α -hydroxy and amino phenylacetic acids. Employing (S)-MPAA (**L17**) as the chiral ligand, the enantio-enriched products were obtained in up to 92% *ee*. Moreover, the recovered starting material could be converted to the other enantiomer in excellent yield and enantioselectivity through Pd-catalyzed C–H olefination using a (R)-MPAA ligand **L18** (Scheme 17).²⁹

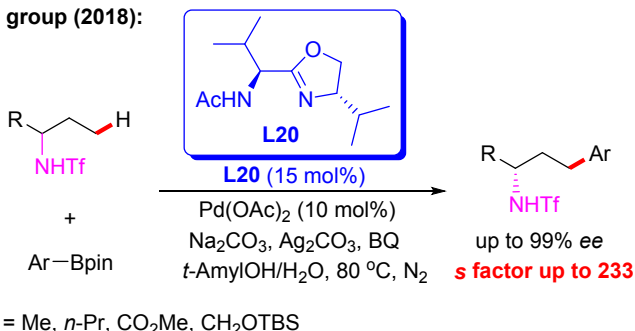
Meanwhile, the Pd(II)-catalyzed asymmetric C–H arylation of Ns-protected benzylamines in the presence of a chiral mono-N-protected α -amino-O-methylhydroxamic acid ligand **L19** has also been achieved via a kinetic resolution process. In this reaction, it is essential to use the easy-to-remove nosyl (Ns) protected amino group as the directing group, and both chiral benzylamines and *ortho*-arylated benzylamines were isolated in excellent enantioselectivities (Scheme 18).³⁰ Very recently, they developed a chiral ligand **L20** for asymmetric γ -C(sp³)–H activation of alkyl amines with ArBpin through a kinetic resolution process (Scheme 19).²⁸

Yu group (2016):



Scheme 18. Kinetic Resolution of Ns-protected benzylamines via a Pd(II)-catalyzed asymmetric C–H arylation

Yu group (2018):



Scheme 19. Pd(II)-catalyzed asymmetric γ -C(sp³)–H activation of alkyl amines with ArBpin through a kinetic resolution process

Axially chiral biaryls are widely present in natural products as the important skeletons.³¹ Moreover, they can also be used as chiral organic catalysts or chiral ligands in asymmetric synthesis.³² The Murai group

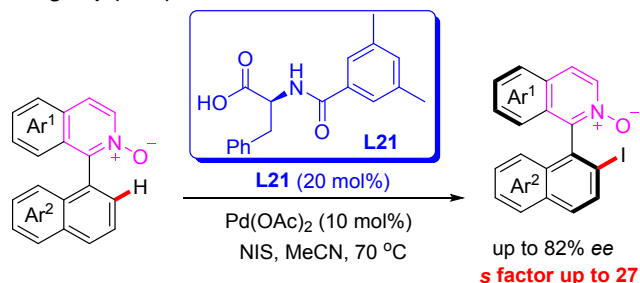
reported the first example of asymmetric C(sp²)–H alkylation of naphthylpyridine derivatives employing chiral ferrocenyl phosphine ligand through Rh(I)-catalyzed the dynamic kinetic resolution process, however, only low yields and enantioselectivities were obtained.³³

The first example of Pd-catalyzed atroposelective C–H iodination reaction through a kinetic resolution process was developed by the You group in 2014. In this reaction, *N*-monoprotected phenylalanine (**L21**), as the most effective chiral ligand, was used to construct axially chiral biaryls in good yields and enantioselectivities (Scheme 20).³⁴

Moreover, the Yang group reported a Pd-catalyzed atroposelective C–H olefination for the construction of axially chiral biaryls in 2017 (Scheme 21). Using P(O)Ph₂ as the directing group and Boc-L-Val-OH (**L14**) as the chiral ligand, the racemic biaryl phosphine oxides were transformed to the desired chiral biaryl phosphine–olefin products in excellent yields (up to 99%) and enantioselectivities (up to 96% *ee*). In addition, both electron-donating and electron-withdrawing substituents on the aromatic rings were well tolerated in this catalytic system.³⁵

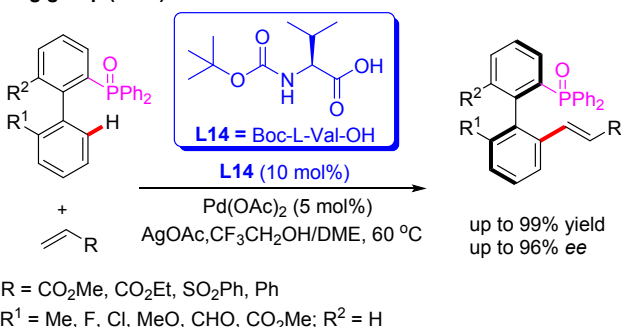
Very recently, Pd-catalyzed atroposelective C–H olefination for the synthesis of axially chiral biaryls by using a novel chiral spiro phosphoric acid ligand **L22**, was developed by Shi and co-workers (Scheme 22a).³⁶ Various axially chiral quinolines were isolated in excellent yields (up to 99 % yields) and enantioselectivities (up to 98 % *ee*). Subsequently, they reported a NH₂-directed Pd-catalyzed atroposelective C–H olefination for the preparation of axially chiral biaryl-2-amines (Scheme 22b).³⁷ In this strategy, chiral spiro phosphoric acid **L23** was used as an efficient ligand to access a broad range of axially chiral biaryl-2-amines in excellent yields (up to 91 %) and enantioselectivities (up to 97% *ee*). During the course, they also developed a novel approach to construct axially chiral styrenes via a Pd(II)-catalyzed atroposelective C–H alkenylation and alkylation by employing L-pyrogutamic acid **L24** as a chiral ligand (Scheme 23).³⁸

You group (2014):



Scheme 20. Pd(II)-catalyzed atroposelective C–H iodination reaction through a kinetic resolution process

Yang group (2017):

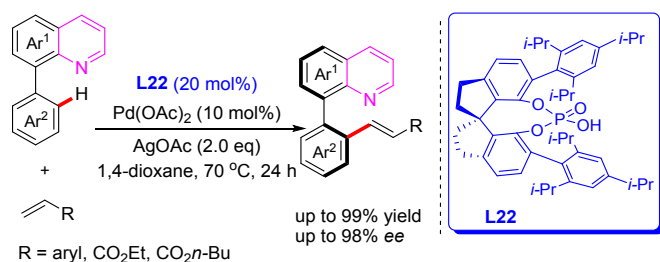


Scheme 21. Pd(II)-catalyzed atroposelective C–H olefination for the construction of axially chiral biaryls



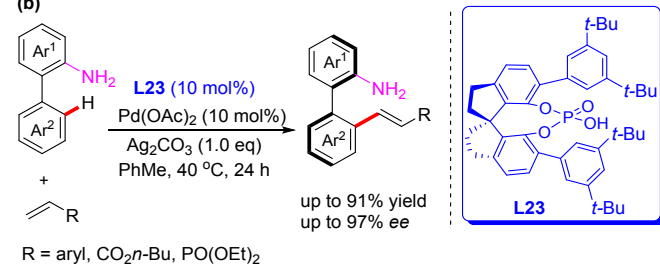
Shi group (2019):

(a)



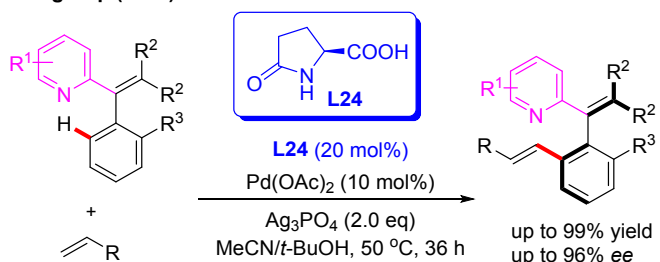
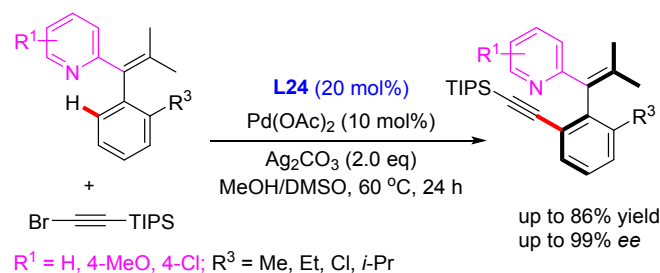
Shi group (2020):

(b)



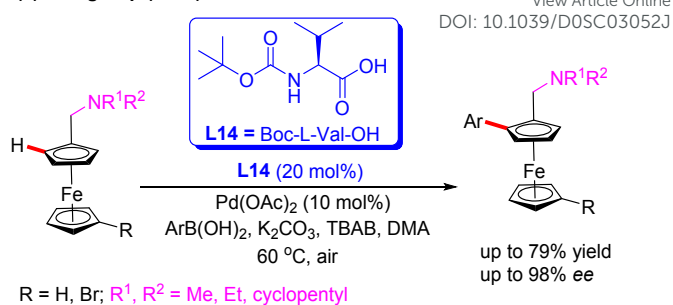
Scheme 22. Pd(II)-catalyzed atroposelective C–H olefination for the synthesis of axially chiral biaryls

Shi group (2020):

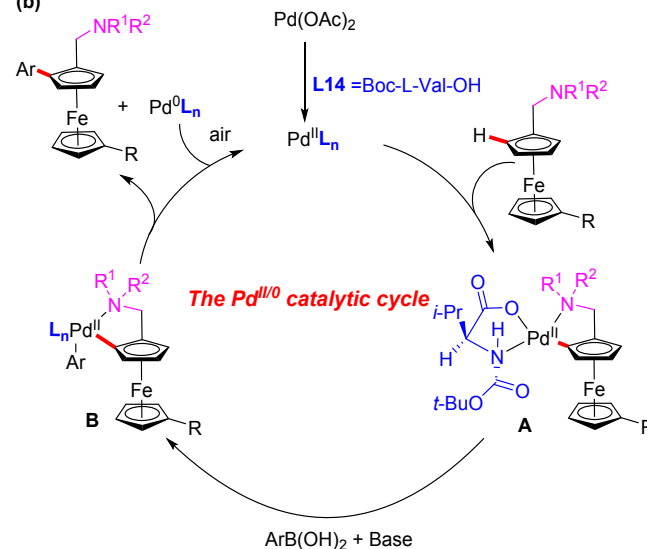
 $\text{R}^1 = \text{H}, 4\text{-Me}, 3\text{-Cl}, 3\text{-CF}_3; \text{R}^2 = \text{Me}, \text{Et}, n\text{-Pr}; \text{R}^3 = \text{Me}, \text{Cl}, i\text{-Pr}$ $\text{R} = \text{CO}_2n\text{-Bu}, \text{CHO}, \text{COEt}, 4\text{-MeOC}_6\text{H}_4, \text{PO}(\text{OEt})_2$ 

Scheme 23. Pd(II)-catalyzed atroposelective C–H olefination for the synthesis of axially chiral biaryls

(a) You group (2013):



(b)

Scheme 24. Pd(II)-catalyzed asymmetric C–H arylation of *N,N*-disubstituted dialkylaminomethyl ferrocenes

Ferrocenes bearing planar chirality have received much attention due to its application in asymmetric catalysis as efficient ligands or catalysts.³⁹ In the field of Pd-catalyzed asymmetric C–H bond functionalization, the Yu group developed a series of by using a catalytic amount of chiral monoprotected amino acids.⁸ Inspired by Yu's work on asymmetric C–H bond functionalization reactions, the You group realized the first example of Pd-catalyzed asymmetric C–H arylation of *N,N*-disubstituted dialkylaminomethyl ferrocenes in 2013 by using Boc-L-Val-OH (**L14**) as the chiral ligand and arylboronic acids as coupling reagents (Scheme 24a).⁴⁰ The desired chiral products were obtained in good yields and excellent enantioselectivities under mild reaction conditions. Notably, with methylboronic acid as the coupling partner, the yield of desired product was dramatically decreased (14%) under even a higher temperature and prolonged reaction time.

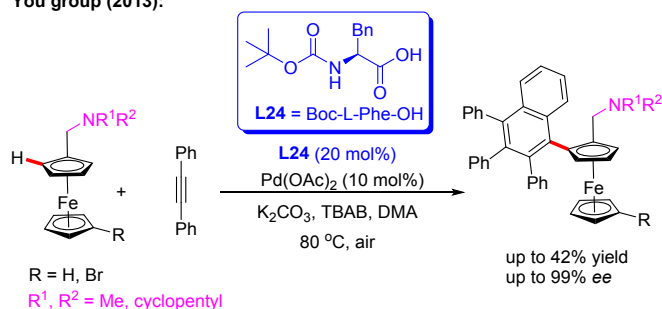
The plausible catalytic cycle involved a Pd(II)/Pd(0) catalysis was depicted in Scheme 24b. The selective C–H bond cleavage of ferrocene with Boc-L-Val-OH and Pd catalyst provides the cyclic Pd(II) intermediate **A**. Subsequent transmetalation between intermediate **A** and aryl boronic acid forms the intermediate **B**. The reductive elimination of the intermediate **B** affords the desired chiral product.

Additionally, they developed another efficient method for the synthesis of planar chiral arylated-ferrocenes through the Pd(II)-catalyzed asymmetric oxidative annulation of *N,N*-disubstituted dialkylaminomethyl ferrocenes with diphenylacetylene by using a chiral

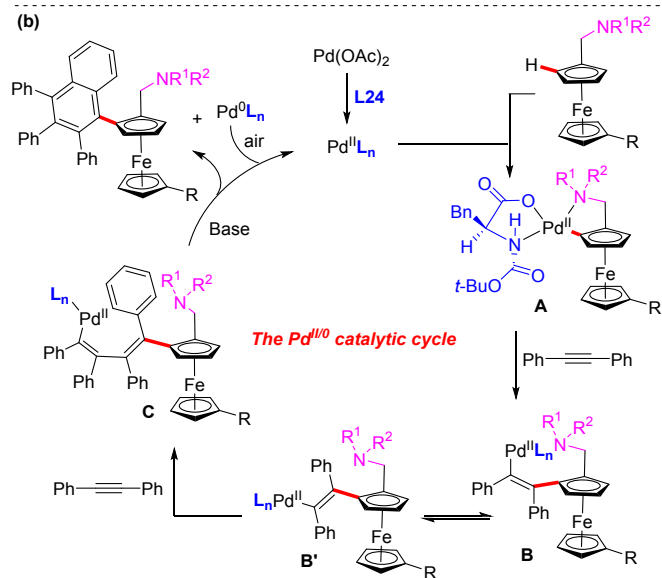


ligand **L24** (Scheme 25a).⁴¹ The reaction mechanism was also proposed as shown in Scheme 25b. First, the cyclic Pd(II) intermediate **A** is generated through coordination of the *N*-atom of the ferrocene derivative to the chiral Pd(II) catalyst followed by site-selective C–H palladation. Next, *syn*-insertion of diphenylacetylene to the intermediate **A** gives the intermediate **B**, which can be further transformed to its trans-isomer **B'**. Subsequently, the second diphenylacetylene molecule is inserted, affording the intermediate **C**. Finally, the desired product is formed through a sequential intramolecular 5-exo-dig insertion, migration and reductive elimination process. Moreover, You and coworkers utilized a Pd(OAc)₂/Boc-L-Ile-OH (**L25**) catalytic system to achieve the highly efficient asymmetric oxidative cross-coupling reaction between ferrocenes and electron-rich heteroarenes in 2016 (Scheme 26).⁴²

You group (2013):



(b)



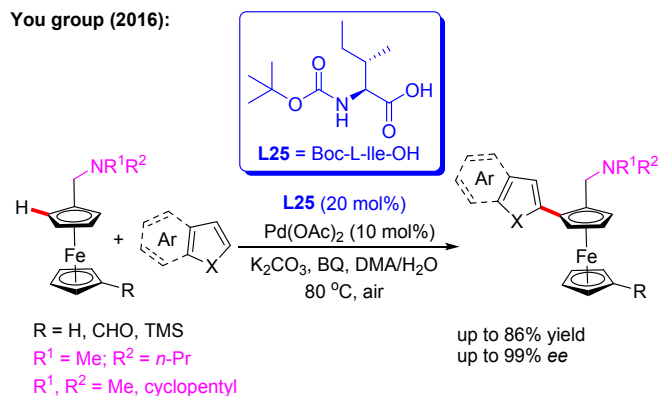
Scheme 25. Pd(II)-catalyzed asymmetric oxidative annulation of *N,N*-disubstituted dialkylaminomethyl ferrocenes with diphenylacetylene

In 2013, the Pd(II)-catalyzed asymmetric oxidative Heck reaction for the efficient synthesis of planar chiral ferrocenes in the presence of a chiral ligand **L24** was also developed by the Cui and Wu group (Scheme 27a).⁴³ In this process, a variety of olefins, such as acrylates, substituted styrenes, vinyl cyclohexanes, and acrylamides, were used to prepare the alkenylation products in excellent yields and enantioselectivities.

Later, they demonstrated a novel catalytic asymmetric C–H acylation reaction in the presence of Pd(OAc)₂ catalyst and Ac-L-Phe-OH (**L26**) (Scheme 27b).⁴⁴ Diaryldiketones bearing either an electron-withdrawing or electron-donating group were well suited for this strategy, and

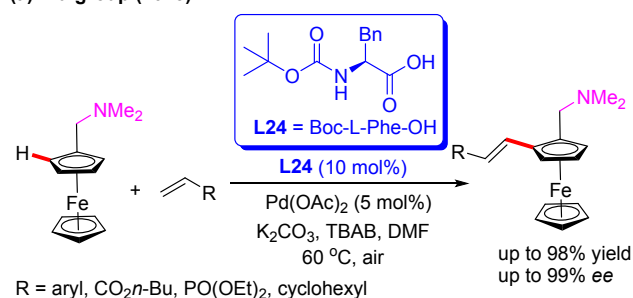
produced various planar chiral ferrocenes in excellent yields and enantioselectivities. During the investigation of the reaction mechanism, they found that the radical scavenger TEMPO inhibited the process. Thus, a radical mechanistic pathway was proposed in Scheme 28. The initiated selective C–H bond cleavage of *N,N*-dimethyl aminomethyl ferrocene in the presence of the Pd(II) catalyst and Ac-L-Phe-OH provides the cyclopalladated intermediate **A**. Meanwhile, the reaction of diaryldiketone with TBHP also provides the radical **B**. The subsequent radical addition reaction of species **B** to the intermediate **A** generates the Pd(III or VI) intermediate **C**. The desired chiral acylated product was then produced via a reductive elimination process.

You group (2016):

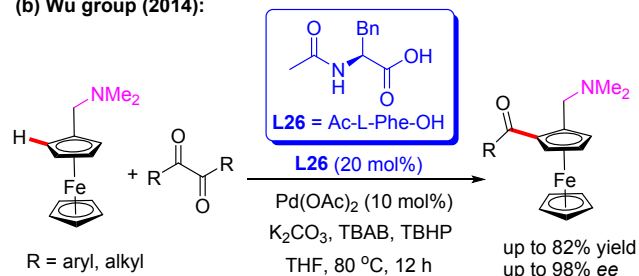


Scheme 26. Pd(II)-catalyzed asymmetric oxidative cross-coupling reaction between ferrocenes and heteroarenes

(a) Wu group (2013):

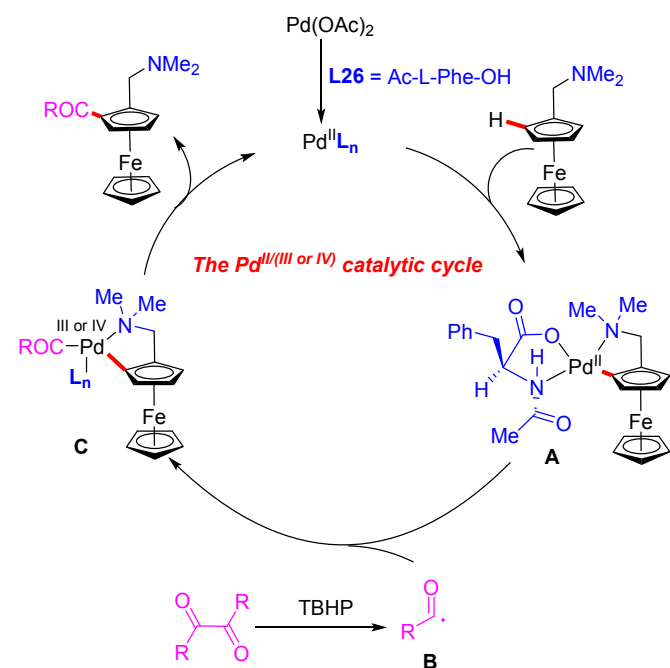


(b) Wu group (2014):



Scheme 27. Pd(II)-catalyzed asymmetric oxidative Heck and acylation reaction

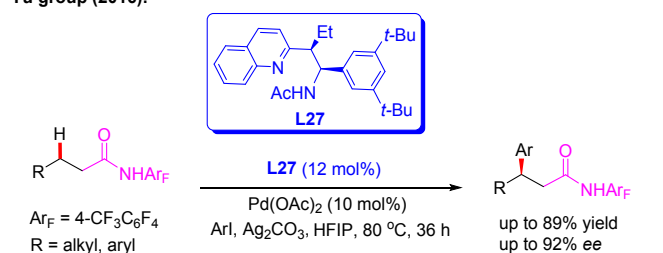




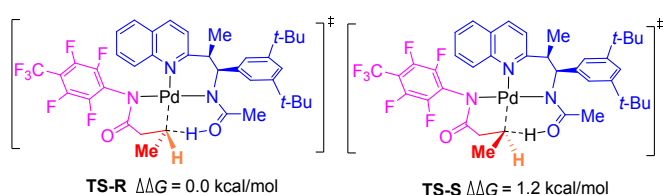
Scheme 28. The proposed mechanistic pathway

As discussed above, significant progress has been made on monodentate directing groups assisted asymmetric C–H functionalization using chiral amino acid or aminomethyl heterocycle ligands. However, only few applicable direct enantioselective functionalization reactions of linear methylene C(sp³)–H bonds have been reported. In 2016, the direct Pd-catalyzed enantioselective arylation of a linear methylene C(sp³)–H bond was achieved by the Yu group (Scheme 29).⁴⁵ The combination of a weakly coordinating 4-trifluoromethyltetrafluorophenyl amide directing group with a chiral acetyl-protected aminoethyl quinolone (APAQ) ligand **L27** proved to be crucial and produced the desired chiral products in good yields (up to 89% yield) and enantioselectivity (up to 92% ee). Moreover, density functional theory (DFT) studies on the observed enantioselectivity in the CMD step were carried out and the results indicated that **TS-R** is more favorable than **TS-S**.

Yu group (2016):



DFT-optimized structures and relative free energies:



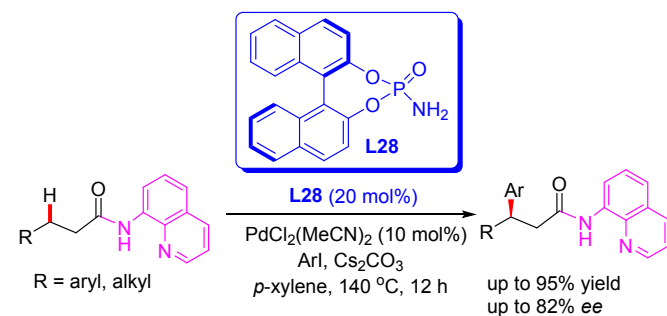
Scheme 29. Pd(II)-catalyzed enantioselective arylation of the linear methylene C(sp³)–H bond activation
View Article Online
DOI: 10.1039/D0SC03052J

3. Bidentate directing group-enabled asymmetric C–H functionalization

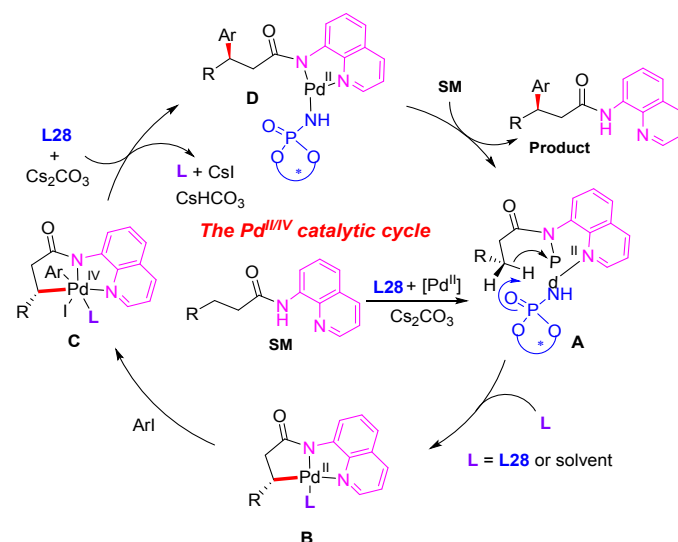
Since the *N,N*-bidentate aminoquinoline (8-aminoquinoline) was firstly introduced by the Daugulis group, a wide range of transition metal-catalyzed C(sp³)–H functionalization reactions have been developed in recent years.⁴⁶ A bidentate directing group often exhibits higher reactivity than a monodentate directing group. However, it is much more difficult to exert chiral induction because there is only a single available coordination site on the metal center.

In 2015, the first example of Pd(II)-catalyzed 8-aminoquinoline (AQ)-assisted enantioselective methylene C(sp³)–H arylation of 3-substituted propanamides was reported by Duan and co-workers employing a chiral BINOL phosphoramidate ligand **L28**. An array of chiral β,β -diaryl carboxylic derivatives were generated in moderate to good enantioselectivities. The mechanistic studies indicated that the chiral phosphoric amide **L28** could accelerate the reaction rate and control the reaction enantioselectivity (Scheme 30).⁴⁷

Duan group (2015):



Scheme 30. Pd(II)-catalyzed and 8-aminoquinoline-assisted enantioselective methylene C(sp³)–H arylation of 3-substituted propanamides



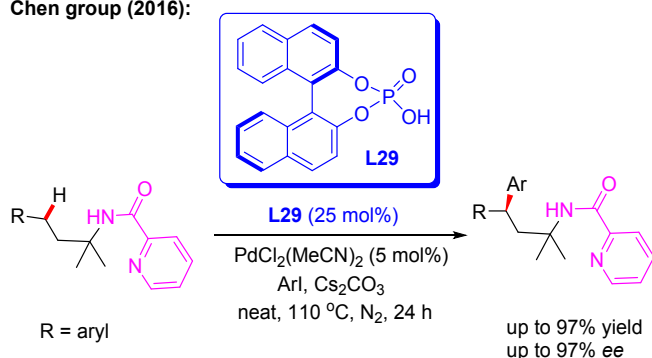
Scheme 31. A plausible catalytic cycle



A plausible catalytic cycle was then proposed in Scheme 31. The ligand exchange of the Pd(II) catalyst with 3-substituted propanamide in the presence of a chiral phosphoric amide **L28** and base Cs_2CO_3 provides the cyclic Pd(II) intermediate **A**. Diastereoselective cyclometalation of this intermediate gives rise to a [5,5]-bicyclic Pd(II) intermediate **B** via a site-selective C–H bond activation process. Oxidative addition of the intermediate **B** with an aryl iodide generates the Pd(IV) species **C**. Subsequent reductive elimination of the palladium complex **C** produces the intermediate **D**, which produces the desired product via the ligand exchange with 3-substituted propanamide.

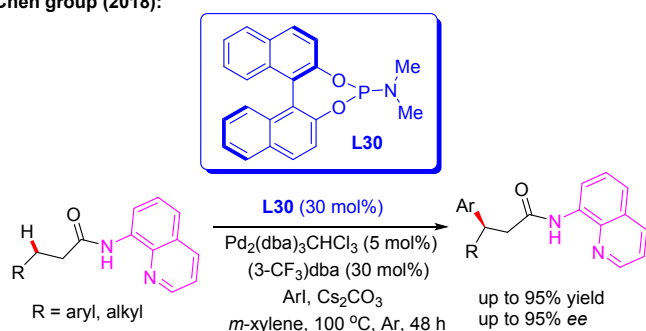
In 2016, Chen and co-workers illustrated a picolinamide (PA)-directed Pd(II)-catalyzed enantioselective γ -C(sp³)-H arylation of 3-arylpropylamines with aryl iodides using the BINOL phosphoric acid ligand **L29** (Scheme 32).⁴⁸ For the first time, the chiral β,β -diaryl-3-propylamines were achieved in excellent yields (up to 97%) and enantioselectivities (up to 97% *ee*). Mechanistic studies indicated that combination of the BINOL phosphoric acid ligand **L29** and Cs_2CO_3 in the absence of solvents gave the highly optically enriched products.

Chen group (2016):



Scheme 32. PA-directed and Pd(II)-catalyzed enantioselective γ -C(sp³)-H arylation of 3-arylpropylamines

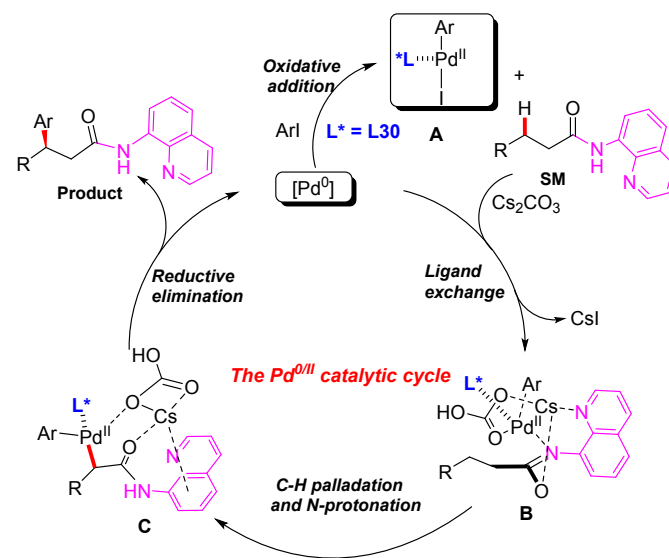
Chen group (2018):



Scheme 33. AQ-mediated and Pd(0)-catalyzed enantioselective β -C(sp³)-H arylation of 3-arylpropylamines

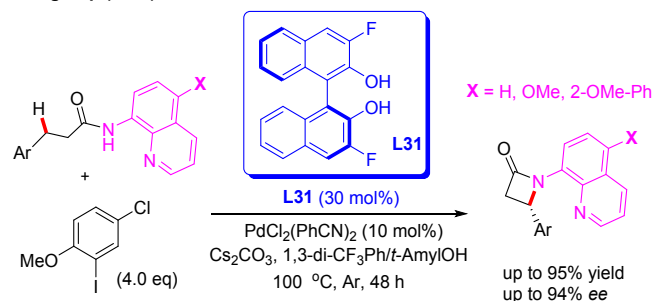
Later, the same group introduced a novel protocol for AQ-mediated Pd(0)-catalyzed enantioselective β -C(sp³)-H arylation of 3-substituted propanamides in the presence of the BINOL phosphoric amide ligand **L30** (Scheme 33).⁴⁹ Compared with the Duan's work, this is the first example of AQ-directed processes involving a Pd(0/II) catalytic cycle, providing the chiral desired products in good yields and enantioselectivities (up to 95% *ee*). Furthermore, the control reactions and DFT calculations showed that both the BINOL phosphoric amide ligand **L30** and Cs_2CO_3 were involved

in the enantio-determining C(sp³)-H palladation step. Additionally, a plausible Pd(0/II) catalytic cycle was proposed (Scheme 34). Oxidation of the Pd(0) catalyst with ArI in the presence of the chiral phosphoric amide **L30** produces the Pd(II) intermediate **A**. Subsequently, the intermediate **B** is formed through a ligand exchange process of the intermediate **A** with AQ-coupled substrate in the presence of Cs_2CO_3 . The diastereoselective C–H palladation and protonation affords the palladium intermediate **C** which provides the desired product upon reductive elimination.



Scheme 34. A plausible Pd(0/II) catalytic cycle

Chen group (2019):



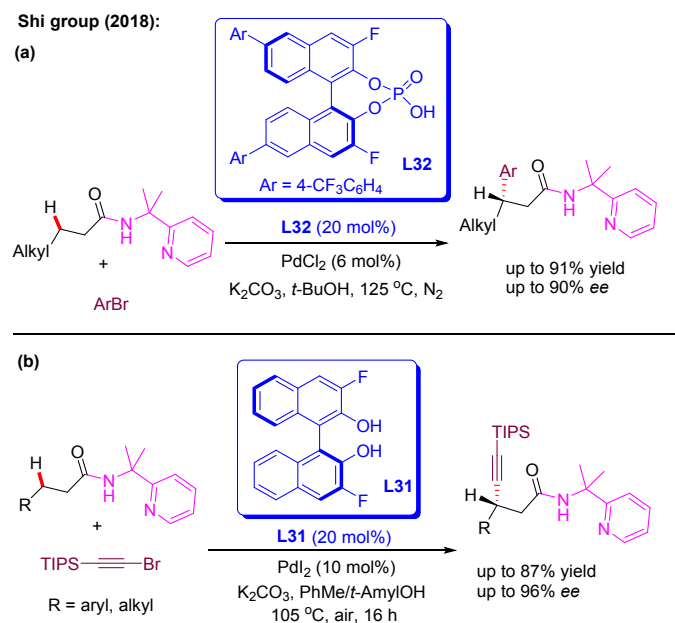
Scheme 35. Pd(II)-catalyzed enantioselective intramolecular β -C(sp³)-H amidation of 3-substituted propanamides

Very recently, the Chen group reported a Pd(II)-catalyzed enantioselective intramolecular β -C(sp³)-H amidation reaction of 3-substituted propanamides for the synthesis of chiral β -aryl- β -lactams. With this novel method, the desired products could be obtained up to 94% *ee* in the presence of the chiral 3,3'-F₂-BINOL ligand **L31**. The control experiments suggested that 2-methoxy-5-chlorophenyl iodide, as the critical oxidant, controls the competing C–C versus C–N reductive elimination pathway of the Pd(IV) intermediate due to its steric and electronic effect (Scheme 35).⁵⁰

The bidentate directing group, 2-(pyridine-yl)isopropyl amine (PIP), was originally designed by the Shi group for the activation of methylene C(sp³)-H bond.⁵¹ Very recently, the group developed the first example of Pd(II)-catalyzed enantioselective functionalization reactions of linear



methylene C(sp³)-H bonds by using the cooperative effects between the PIP group and chiral phosphoric acid ligand **L32** (Scheme 36a).⁵² With aryl bromides as the less reactive arylating reagents, a variety of 3-alkylpropanamides were readily arylated and provided the desired product in excellent yields (up to 96%) and good enantioselectivities (up to 90% *ee*). Later, the same group realized the first example of PIP-assisted Pd(II)-catalyzed enantioselective methylene C(sp³)-H alkylation of 3-alkyl and 3-aryl propanamides employing the chiral 3,3'-F₂-BINOL ligand **L31**. The control experiments suggested that the superior effect of PIP than AQ existed in this alkylation reaction (Scheme 36b).⁵³



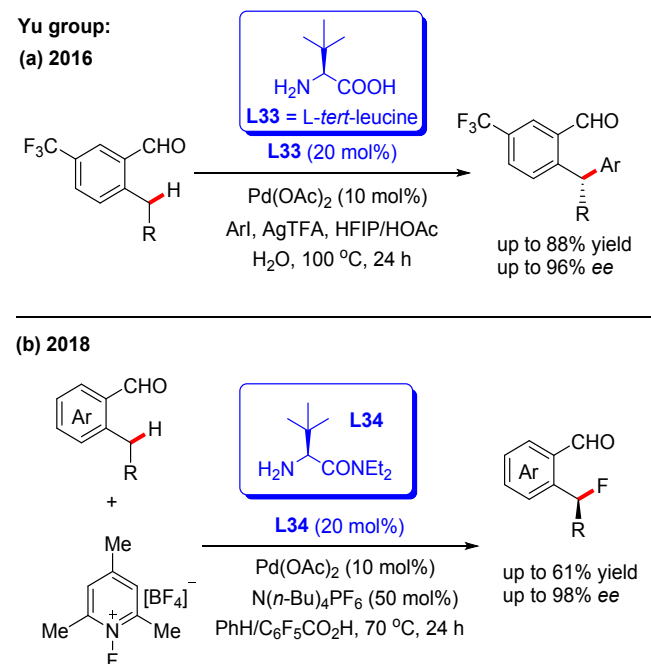
Scheme 36. Pd(II)-catalyzed enantioselective functionalization of linear methylene C(sp³)-H bonds enabled by a PIP group

4. Transient directing group-enabled asymmetric C-H functionalization

Pd-catalyzed asymmetric C(sp²)-H and C(sp³)-H bond functionalization reactions have been well documented by employing a directing group and external chiral ligand. However, a major issue exists in this strategy: pre-installation and removal of the directing group.⁸⁻¹¹ Thus, a promising approach of developing the Pd-catalyzed asymmetric C-H functionalization would be the utilization of a chiral transient directing group. In order to achieve this asymmetric process, two issues need to be taken into consideration: (1) the chiral center is usually far away from the targeted C-H bond, which may result in low enantioselectivity; (2) the free chiral transient ligand could coordinate to the metal center, which may lead to the opposite asymmetric induction.^{8b}

The first example Pd(II)-catalyzed chiral transient ligand-enabled asymmetric C(sp³)-H bond functionalization of *ortho*-alkylbenzaldehydes was developed by Yu and co-workers in 2016 (Scheme 37a).⁷ Using *L*-tert-Leucine (**L33**) as the chiral transient directing group, Pd(II)-catalyzed enantioselective benzylic C(sp³)-H arylation was demonstrated. Under the optimal conditions, 2-ethyl-5-(trifluoromethyl)-benzaldehyde was arylated with methyl 4-iodobenzoate to provide the desired chiral product with 96% *ee*. Subsequently, the same group disclosed a Pd(II)-catalyzed enantioselective C(sp³)-H fluorination of *ortho*-

alkylbenzaldehydes in the presence of the chiral directing group **L34**. The detailed mechanistic studies showed that **L34** bearing a bulky group played an important role for promoting C-F reductive elimination and achieving a high enantioselectivity (Scheme 37b).⁵⁴

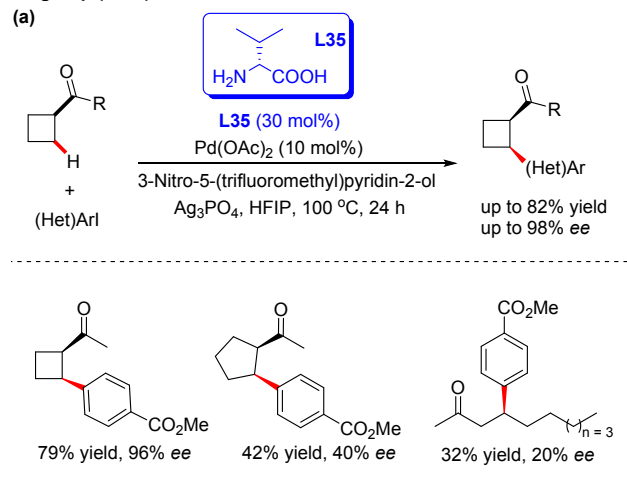


Scheme 37. Pd(II)-catalyzed asymmetric C(sp³)-H bond functionalization of *ortho*-alkylbenzaldehydes

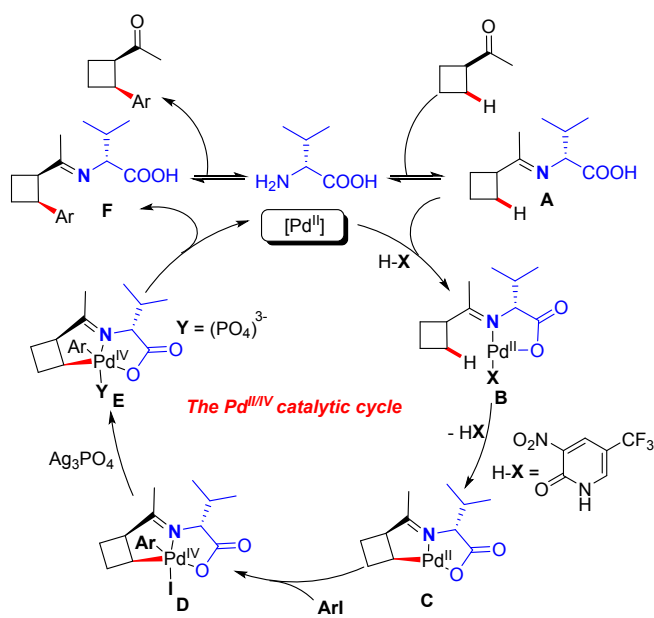
Very recently, the first example of Pd(II)-catalyzed asymmetric C(sp³)-H arylation of ketones employing D-valine (**L35**) as a chiral transient directing group was reported by the Yu group. The control experiments suggested that both the 3-nitro-5-trifluoromethyl-2-pyridone ligand and Ag₃PO₄ additive play crucial roles in this asymmetric desymmetrization of cyclobutyl ketones. However, when using cyclopentyl ketones and linear ketones as the starting materials, the results were not satisfactory (Scheme 38a).⁵⁵ A plausible mechanism was proposed in Scheme 38b. It was envisioned that the process is initiated with reversible imine formation from 1-cyclobutylethanone with chiral directing group D-valine, providing the imine intermediate **A**. Coordination of the intermediate **A** to the Pd(II) species followed by a ligand exchange process with 3-nitro-5-trifluoromethyl-2-pyridone generates the palladium complex **B**. Cyclopalladation of the intermediate **B** generates the [5,5]-bicyclic intermediate **C** through a concerted metallation-deprotonation (CMD) process. Oxidative addition of the intermediate **C** with an aryl iodide affords the Pd(IV) complex **D**. In the presence of Ag₃PO₄, reductive elimination of this Pd complex provides the intermediate **F**, which releases the final chiral product and D-valine.



Yu group (2020):



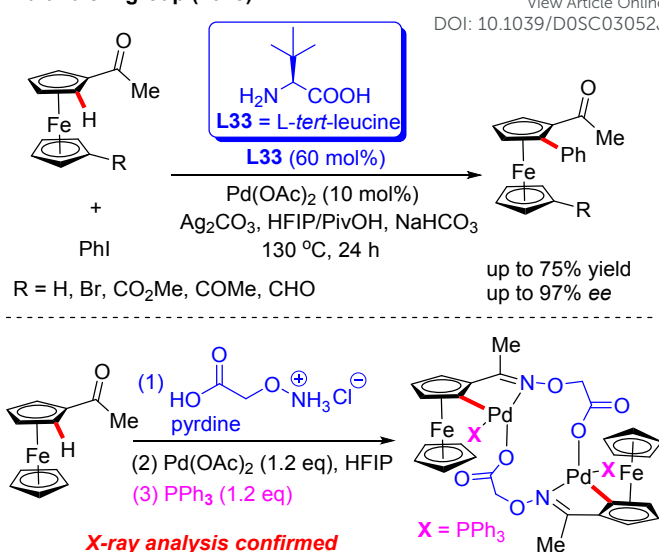
(b) a plausible mechanism:



Scheme 38. Pd(II)-catalyzed asymmetric C(sp³)-H arylation of ketones employing D-valine as a chiral transient directing group

Inspired by the Yu's work, the Xu and Jin group demonstrated the Pd-catalyzed asymmetric C-H arylation of ferrocenyl ketones through a dynamic kinetic resolution process by using commercially available *L*-tert-leucine (**L33**) as the chiral transient directing group (Scheme 39).⁵⁶ The absolute configuration of chiral arylated ferrocenyl ketones were assigned to *R_p* though the single crystal X-ray diffraction analysis. This strategy provides a complementary approach to the synthesis of various novel and important planar chiral ferrocenyl-phosphine ligands. In the presence of stoichiometric amounts of PPh₃, di-cyclopalladated intermediate was isolated from the reaction of acetylferrocene, Pd(OAc)₂ and 2-(aminooxy)acetic acid hydrochloric salt, and structure of this intermediate was further confirmed by X-ray analysis.

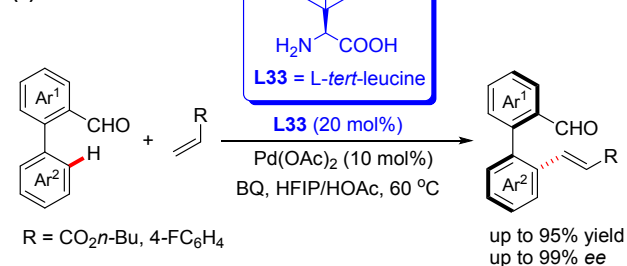
Xu and Jin group (2018):



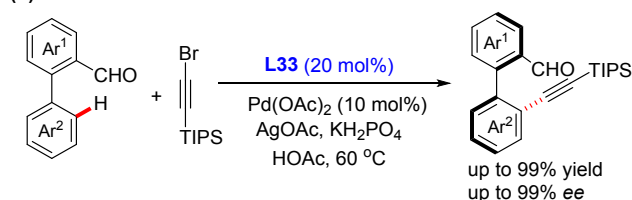
Scheme 39. Pd(II)-catalyzed asymmetric C-H arylation of ferrocenyl ketones enabled by a transient directing group *L*-tert-leucine

Shi group:

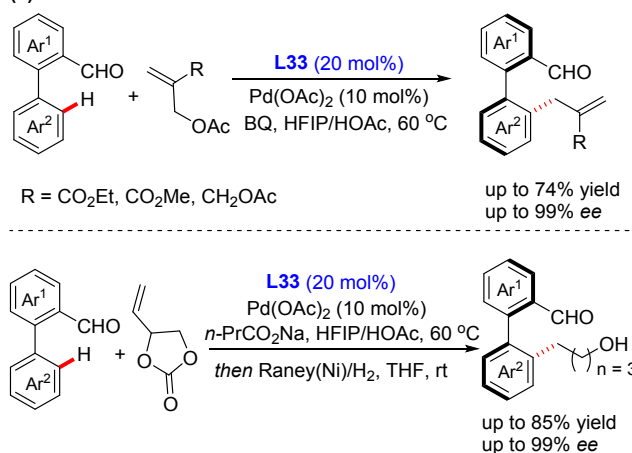
(a) 2017



(b) 2018

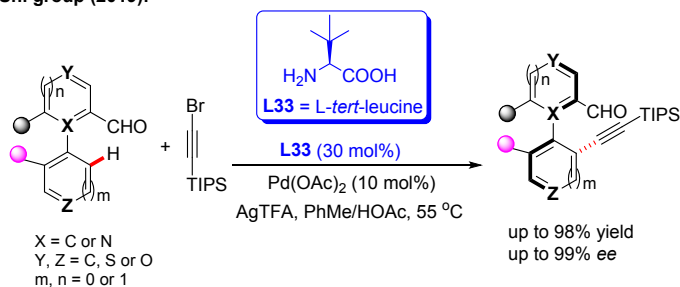


(c) 2018



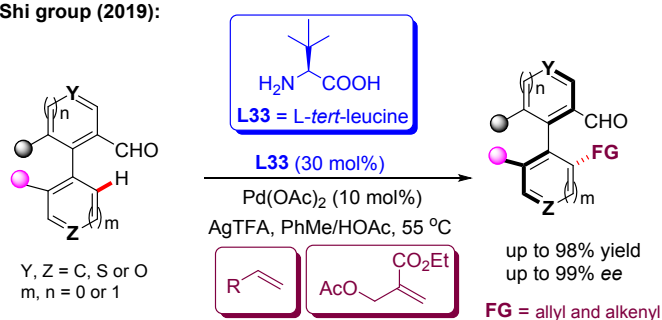
Scheme 40. Pd(II)-catalyzed asymmetric C–H bond functionalization for the construction of axially chiral biaryl aldehydes

Shi group (2019):



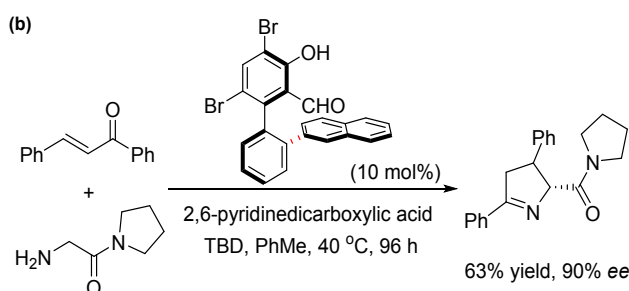
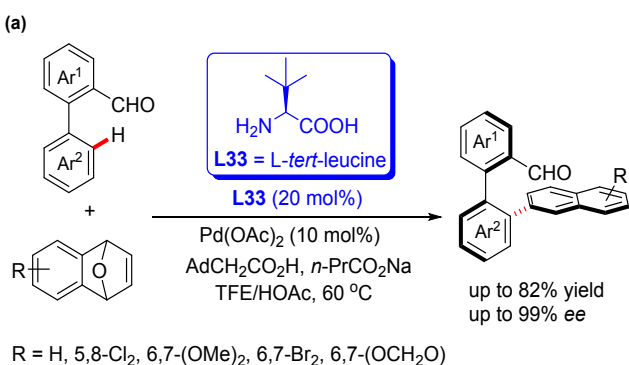
Scheme 41. Pd(II)-catalyzed atroposelective C–H alkynylation for the synthesis of axially chiral heteroaryls

Shi group (2019):



Scheme 42. Pd(II)-catalyzed atroposelective C–H allylation and alkenylation for the synthesis of axially chiral heteroaryls

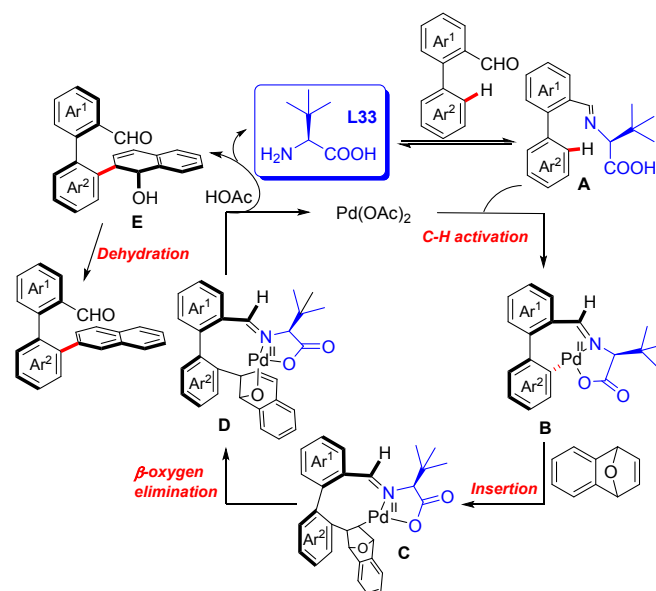
Shi group (2019):



Scheme 43. Pd(II)-catalyzed asymmetric C–H naphthylation with 7-oxabenzonornbornadienes and its application

In the meantime, using the same chiral transient directing group **L33**, Shi and co-workers realized an efficient method for the construction of axially chiral biaryl aldehydes via a Pd(II)-catalyzed asymmetric C–H bond olefination process (Scheme 40a).⁵⁷ Later, they utilized *L-tert-leucine* (**L33**) as the efficient chiral transient ligand for the Pd(II)-catalyzed asymmetric C–H alkynylation and allylation of biaryl aldehydes (Scheme 40b and 40c).^{58–59} Additionally, they developed the Pd(II)-catalyzed atroposelective C–H alkynylation, allylation and alkenylation for the synthesis of axially chiral heteroaryls by using **L33** as a chiral transient ligand. A wide range of five-membered heteroarenes, including pyrroles, thiophenes, benzothiophenes, and benzofurans, were all compatible with this strategy, providing the axially chiral heteroaryls in good enantioselectivities (Scheme 41 and 42).^{60–61}

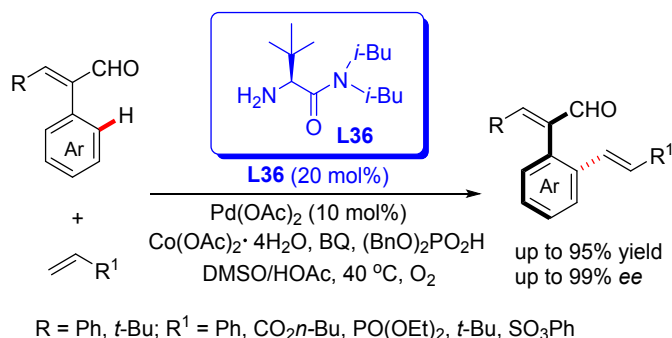
In 2019, the Shi group used this novel asymmetric C–H functionalization strategy for the synthesis of various axially chiral biaryl aldehydes. In the presence of Pd(OAc)₂ and *L-tert-leucine* (**L33**), the atroposelective C–H naphthylation with 7-oxabenzonornbornadienes was achieved in good yields and excellent enantioselectivities (up to 99% ee). Using these synthetic axially chiral aldehydes as the chiral catalysts, the better catalytic activity was exhibited in the asymmetric reaction of glycine derived amides and dipeptides (Scheme 43).⁶² A plausible mechanism was proposed in Scheme 44. First, the reversible imine formation between the biaryl aldehyde and the chiral directing group *L-tert-leucine* affords the imine intermediate **A**. The selective C–H cyclopalladation of the intermediate **A** gives rise to the enantioenriched palladacycle intermediate **B**. Migratory insertion of the palladacycle **B** with 1,4-dihydro-1,4-epoxynaphthalene and subsequent β-oxygen elimination generates the intermediate **D** which releases the intermediate **E**, *L-tert-leucine*, and Pd(II) catalyst through a protonolysis process in the presence of HOAc. Dehydration of the intermediate **E** finally provides the desired product.



Scheme 44. The proposed mechanism



Shi group (2020):



Scheme 45. Pd(II)-catalyzed asymmetric C–H olefination using a bulky chiral amino amide **L36** for the synthesis of axially chiral styrenes

Very recently, the same group reported an efficient and practical method to construct a novel class of axially chiral styrenes through a Pd-catalyzed asymmetric C–H olefination reaction using the bulky amino amide **L36** as a modified chiral transient directing group (Scheme 45).⁶³ This novel method provides a simple, efficient and fast way to synthesize a variety of axially chiral styrene ligands. Moreover, this kind of ligands could also be used to prepare the corresponding chiral acid ligand for the Co(III)-catalyzed asymmetric C(sp³)–H amidation of thioamide.

Conclusions and outlook

In the past decade, transition metal-catalyzed asymmetric C–H functionalization has become a direct and effective method to access various chiral skeletons. In this mini-review, we provided a robust discussion of recent advances on Pd-catalyzed asymmetric C–H functionalization by using different directing groups, including a monodentate, bidentate, and transient directing group. A range of optically active building blocks, such as chiral heterocyclic compounds, chiral amides, chiral carboxylic acids, chiral amines, axially chiral biaryls, and planar chiral ferrocenes, have been obtained through Pd-catalyzed asymmetric C(sp²)–H and C(sp³)–H functionalization with a chiral ligand as a monodentate directing group. Bidentate directing groups (AQ, PA and PIP) exhibit a higher reactivity, which could be used in asymmetric linear methylene C(sp³)–H functionalization in combination with a chiral BINOL ligand. In general, these directing groups often need to be pre-installed on the substrates to promote the asymmetric C–H functionalization reactions, which severely limits the efficiency of the process. More recently, the transient directing strategy has been developed in Pd-catalyzed asymmetric C–H functionalization. While some significant work has been realized by using chiral transient directing groups, there are still many opportunities for improvement and utilization, such as the use of other transition metals and non-covalent bonding modes. We hope this mini-review would provide some insights for readers and inspire them for discovering more innovative strategies in the transition metal-catalyzed asymmetric C–H functionalization reactions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

View Article Online

DOI: 10.1039/D0SC03052J

We gratefully acknowledge NSF (CHE-2029932), Robert A. Welch Foundation (D-2034-20200401), and Texas Tech University for financial support. Ke Yang is grateful for financial support from NSFC: (No. 21702019) and Advanced Catalysis and Green Manufacturing Collaborative Innovation Center, Changzhou University.

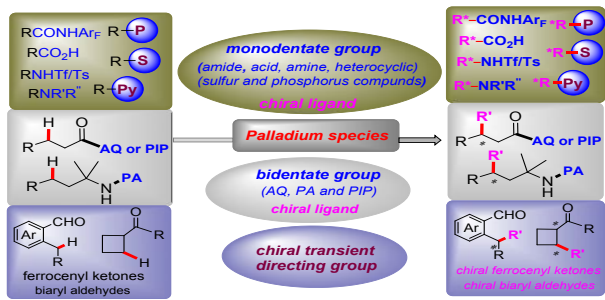
Notes and references

- (a) Y. Yang, J. Lan and J. You, *Chem. Rev.*, 2017, **117**, 8787; (b) J. F. Hartwig, *Acc. Chem. Res.*, 2017, **50**, 549; (c) H. M. L. Davies and D. Morton, *ACS Cent. Sci.*, 2017, **3**, 936; (d) Q.-Z. Zheng and N. Jiao, *Chem. Soc. Rev.*, 2016, **45**, 4590; (e) H. Kim and S. Chang, *ACS Catal.*, 2016, **6**, 2341; (f) J. Miao and H. Ge, *Eur. J. Org. Chem.*, 2015, **2015**, 7859; (g) Z. Huang, H. N. Lim, F. Mo, M. C. Young and G. Dong, *Chem. Soc. Rev.*, 2015, **44**, 7764; (h) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (i) U. Dutta, S. Maiti, S. Pimparkar, S. Maiti, L. R. Gahan, E. H. Krensch, D. W. Lupton and D. Maiti, *Chem. Sci.*, 2019, **10**, 7426; (j) S. Maiti, P. Dolui, R. Kancherla and D. Maiti, *Chem. Sci.*, 2017, **8**, 5181.
- (a) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754; (b) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (c) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094.
- (a) S. Guin, P. Dolui, X. Zhang, S. Paul, V. K. Singh, S. Pradhan, H. B. Chandrashekar, S. S. Anjana, R. S. Paton and D. Maiti, *Angew. Chem., Int. Ed.*, 2019, **58**, 5633; (b) K. Ramakrishna, J. P. Biswas, S. Jana, T. K. Achar, S. Porey and D. Maiti, *Angew. Chem., Int. Ed.*, 2019, **58**, 13808; (c) C. Sambhiago, D. Schönbauer, R. Blicke, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes and M. Schnürch, *Chem. Soc. Rev.*, 2018, **47**, 6603; (d) W.-B. Ma, P. Gandeepan, J. Li and L. Ackermann, *Org. Chem. Front.*, 2017, **4**, 1435; (e) A. Maji, B. Bhaskararao, S. Singha, R. B. Sunoj and D. Maiti, *Chem. Sci.*, 2016, **7**, 3147; (f) Z.-K. Chen, B.-J. Wang, J.-T. Zhang, W.-L. Yu, Z.-X. Liu and Y.-H. Zhang, *Org. Chem. Front.*, 2015, **2**, 1107.
- (a) B. Niu, K. Yang, B. Lawrence and H. Ge, *ChemSusChem*, 2019, **12**, 2955; (b) Q. Zhao, T. Polsson, X. Pannecoucke and T. Besset, *Synthesis*, 2017, **49**, 4808; (c) P. Gandeepan and L. Ackermann, *Chem*, 2018, **4**, 199; (d) T. Bhattacharya, S. Pimparkar and D. Maiti, *RSC Adv.*, 2018, **8**, 19456; (e) S. St John-Campbell, J. Campbell and J. A. Bull, *Org. Biomol. Chem.*, 2018, **16**, 4582.
- (a) J. Loup, U. Dhawa, F. Pesciaoli, J. Wencel-Delord and L. Ackermann, *Angew. Chem., Int. Ed.*, 2019, **58**, 2; (b) Q. Lu and F. Glorius, *Angew. Chem., Int. Ed.*, 2017, **56**, 49; (c) Y. Qin, L. Zhu and S. Luo, *Chem. Rev.*, 2017, **117**, 9433; (d) Y.-N. Ma, S.-X. Li and S.-D. Yang, *Acc. Chem. Res.*, 2017, **50**, 1480; (e) C. Zheng and S.-L. You, *RSC Adv.*, 2014, **4**, 6173; (f) S. K. Murphy and V. M. Dong, *Chem. Commun.*, 2014, **50**, 13645.
- B.-F. Shi, N. Mangel, Y.-H. Zhang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2008, **47**, 4882.
- F.-L. Zhang, K. Hong, T.-J. Li, H. Park and J.-Q. Yu, *Science*, 2016, **351**, 252.
- (a) Q. Shao, K. Wu, Z. Zhuang, S. Qian and J.-Q. Yu, *Acc. Chem. Res.*, 2020, **53**, 833; (b) T. G. Saint-Denis, R.-Y. Zhu, G. Chen, Q.-F. Wu and J.-Q. Yu, *Science*, 2018, **359**, 759.
- (a) J. Huang, Q. Gu and S. You, *Chin. J. Org. Chem.*, 2018, **38**, 51; (b) D.-W. Gao, Q. Gu, C. Zheng and S.-L. You, *Acc. Chem. Res.*, 2017, **50**, 351.
- G. Liao, T. Zhou, Q.-J. Yao and B.-F. Shi, *Chem. Commun.*, 2019, **55**, 8514.
- C. G. Newton, S.-G. Wang, C. C. Oliveira and N. Cramer, *Chem. Rev.*, 2017, **117**, 8908.



- 12 X.-P. Zeng, Z.-Y. Cao, Y.-H. Wang, F. Zhou and J. Zho, *Chem. Rev.*, 2016, **116**, 7330.
- 13 (a) R. Giri, X. Chen and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2005, **44**, 2112; (b) R. Giri, J. Liang, J.-G. Lei, J.-J. Li, D.-H. Wang, X. Chen, I. C. Naggar, C. Guo, B. M. Foxman and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2005, **44**, 7420. (c) B. Bhaskararao, S. Singh, M. Anand, P. Verma, P. Prakash, A. C. S. Malakar, H. F. Schaefer and R. B. Sunoj, *Chem. Sci.*, 2020, **11**, 208; (d) N. Rodriguez and L. J. Goossen, *Chem. Soc. Rev.*, 2011, **40**, 5030.
- 14 B.-F. Shi, Y.-H. Zhang, J. K. Lam, D.-H. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 460.
- 15 M. Wasa, K. M. Engle, D. W. Lin, E. J. Yoo and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 19598.
- 16 K.-J. Xiao, D. W. Lin, M. Miura, R.-Y. Zhu, W. Gong, M. Wasa and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 8138.
- 17 J. He, Q. Shao, Q. Wu and J.-Q. Yu, *J. Am. Chem. Soc.*, 2017, **139**, 3344.
- 18 Q.-F. Wu, X.-B. Wang, P.-X. Shen and J.-Q. Yu, *ACS Catal.*, 2018, **8**, 2577.
- 19 Q.-F. Wu, P.-X. Shen, J. He, X.-B. Wang, F. Zhang, Q. Shao, R.-Y. Zhu, C. Mapelli, J. X. Qiao, M. A. Poss and J.-Q. Yu, *Science*, 2017, **355**, 499.
- 20 G. Xu, C. H. Senanayake and W. Tang, *Acc. Chem. Res.*, 2019, **52**, 1101.
- 21 Z.-J. Du, J. Guan, G.-J. Wu, P. Xu, L.-X. Gao and F.-S. Han, *J. Am. Chem. Soc.*, 2015, **137**, 632.
- 22 P. X. Shen, L. Hu, Q. Shao, K. Hong and J.-Q. Yu, *J. Am. Chem. Soc.*, 2018, **140**, 6545.
- 23 L. Hu, P.-X. Shen, Q. Shao, K. Hong, J. X. Qiao and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2019, **58**, 2134.
- 24 R. Hili and A. K. Yudin, *Nat. Chem. Biol.*, 2006, **2**, 284.
- 25 L. Chu, X.-C. Wang, C. E. Moore, A. L. Rheingold and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 16344.
- 26 K. S. L. Chan, H.-Y. Fu and J.-Q. Yu, *J. Am. Chem. Soc.*, 2015, **137**, 2042.
- 27 P. Jain, P. Verma, G. Xia and J.-Q. Yu, *Nature Chem.*, 2016, **9**, 140.
- 28 Q. Shao, Q.-F. Wu, J. He and J.-Q. Yu, *J. Am. Chem. Soc.*, 2018, **140**, 5322.
- 29 K.-J. Xiao, L. Chu and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2016, **55**, 2856.
- 30 K.-J. Xiao, L. Chu, G. Chen and J.-Q. Yu, *J. Am. Chem. Soc.*, 2016, **138**, 7796.
- 31 (a) J. E. Smyth, N. M. Butler and P. A. Keller, *Nat. Prod. Rep.*, 2015, **32**, 1562; (b) G. Bringmann, T. Gulder, T. A. M. Gulder and M. Breuning, *Chem. Rev.*, 2011, **111**, 563; (c) S. R. LaPlante, L. D. Fader, K. R. Fandrick, D. R. Fandrick, O. Hucke, R. Kemper, S. P. F. Miller and P. J. Edwards, *J. Med. Chem.*, 2011, **54**, 700.
- 32 T. P. Yoon and E. N. Jacobsen, *Science*, 2003, **299**, 1691.
- 33 F. Kakiuchi, P. L. Gendre, A. Yamada, H. Ohtaki and S. Murai, *Tetrahedron: Asymmetry*, 2000, **11**, 2647.
- 34 D.-W. Gao, Q. Gu and S.-L. You, *ACS Catal.*, 2014, **4**, 2741.
- 35 S.-X. Li, Y. N. Ma and S.-D. Yang, *Org. Lett.*, 2017, **19**, 1842.
- 36 J. Luo, T. Zhang, L. Wang, G. Liao, Q.-J. Yao, Y.-J. Wu, B.-B. Zhan, Y. Lan, X.-F. Lin and B.-F. Shi, *Angew. Chem., Int. Ed.*, 2019, **58**, 6708.
- 37 B.-B. Zhan, L. Wang, J. Luo, X.-F. Lin and B.-F. Shi, *Angew. Chem., Int. Ed.*, 2020, **59**, 3568.
- 38 L. Jin, Q.-J. Yao, P.-P. Xie, Y. Li, B.-B. Zhan, Y.-Q. Han, X. Hong and B.-F. Shi, *Chem*, 2020, **6**, 497.
- 39 T. Noël and J. Van der Eycken, *Green Process. Synth.*, 2013, **2**, 297.
- 40 D.-W. Gao, Y.-C. Shi, Q. Gu, Z.-L. Zhao and S.-L. You, *J. Am. Chem. Soc.*, 2013, **135**, 86.
- 41 Y.-C. Shi, R.-F. Yang, D.-W. Gao and S.-L. You, *Beilstein J. Org. Chem.*, 2013, **9**, 1891.
- 42 D.-W. Gao, Q. Gu and S.-L. You, *J. Am. Chem. Soc.*, 2016, **138**, 2544.
- 43 C. Pi, Y. Li, X.-L. Cui, H. Zhang, Y.-B. Han and Y.-J. Wu, *Chem. Sci.*, 2013, **4**, 2675. view Article Online
DOI: 10.1039/D0SC03052J
- 44 C. Pi, X.-L. Cui, X.-Y. Liu, M. X. Guo, H.-Y. Zhang and Y.-J. Wu, *Org. Lett.*, 2014, **16**, 5164.
- 45 G. Chen, W. Gong, Z. Zhuang, M. S. Andr , Y.-Q. Chen, X. Hong, Y.-F. Yang, T. Liu, K. N. Houk and J.-Q. Yu, *Science*, 2016, **353**, 1023.
- 46 (a) S. Rej, Y. Ano and N. Chatani, *Chem. Rev.*, 2020, **120**, 1788; (b) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726; (c) D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2010, **132**, 3965.
- 47 S.-B. Yan, S. Zhang and W.-L. Duan, *Org. Lett.*, 2015, **17**, 2458.
- 48 (a) H. Wang, H.-R. Tong, G. He and G. Chen, *Angew. Chem., Int. Ed.*, 2016, **55**, 15387; (b) O. Daugulis, J. Roane and L. D. Tran, *Acc. Chem. Res.*, 2015, **48**, 1053.
- 49 H.-R. Tong, S. Zheng, X. Li, Z. Deng, H. Wang, G. He, Q. Peng and G. Chen, *ACS Catal.*, 2018, **8**, 11502.
- 50 H.-R. Tong, W. Zheng, X. Lv, G. He, P. Liu and G. Chen, *ACS Catal.*, 2020, **10**, 114.
- 51 Q. Zhang and B.-F. Shi, *Chin. J. Chem.*, 2019, **37**, 647.
- 52 S.-Y. Yan, Y.-Q. Han, Q.-J. Yao, X.-L. Nie, L. Liu, B.-F. Shi, *Angew. Chem. Int. Ed.*, 2018, **57**, 9093.
- 53 Y.-Q. Han, Y. Ding, T. Zhou, S.-Y. Yan, H. Song, B.-F. Shi, *J. Am. Chem. Soc.*, 2019, **141**, 4558.
- 54 H. Park, P. Verma, K. Hong and J.-Q. Yu, *Nature Chem.*, 2018, **10**, 755.
- 55 L.-J. Xiao, K. Hong, F. Luo, L. Hu, W. R. Ewing, K.-S. Yeung and J.-Q. Yu, *Angew. Chem. Int. Ed.*, 2020, 10.1002/anie.202000532.
- 56 J.-C. Xu, Y. Liu, J.-L. Zhang, X.-H. Xu and Z. Jin, *Chem. Commun.*, 2018, **54**, 689.
- 57 J. Yao, S. Zhang, B.-B. Zhan and B.-F. Shi, *Angew. Chem. Int. Ed.*, 2017, **56**, 6617.
- 58 G. Liao, B. Li, H.-M. Chen, Q.-J. Yao, Y.-N. Xia, J. Luo and B.-F. Shi, *Angew. Chem. Int. Ed.*, 2018, **57**, 17151.
- 59 G. Liao, Q.-J. Yao, Z.-Z. Zhang, Y.-J. Wu, D.-Y. Huang and B.-F. Shi, *Angew. Chem. Int. Ed.*, 2018, **57**, 3661.
- 60 H.-M. Chen, S. Zhang, G. Liao, Q.-J. Yao, X.-T. Xu, K. Zhang and B.-F. Shi, *Organometallics*, 2019, **38**, 4022.
- 61 S. Zhang, Q.-J. Yao, G. Liao, X. Li, H. Li, H.-M. Chen, X. Hong and B.-F. Shi, *ACS Catal.*, 2019, **9**, 1956.
- 62 G. Liao, H.-M. Chen, Y.-N. Xia, B. Li, Q.-J. Yao and B.-F. Shi, *Angew. Chem. Int. Ed.*, 2019, **58**, 11464.
- 63 H. Song, Y. Li, Q.-J. Yao, L. Jin, L. Liu, Y.-H. Liu and B.-F. Shi, *Angew. Chem. Int. Ed.*, 2020, **59**, 6576.





This minireview introduces Pd-catalyzed direct asymmetric C–H functionalization reactions using a directing group strategy.

