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Trends in Chemistry

Review

Palladium-catalyzed enantioselective C–H functionalization via C–H palladation

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Transition-metal-catalyzed enantioselective C–H bond activation has emerged as an increasingly important tool for the expedient synthesis of complex chiral molecules. In the past decade, palladium, one of the most commonly employed metal catalysts, has attracted significant attention in enantioselective C–H functionalization for its great promise to streamline the synthesis of chiral molecules and inspired new retrosynthetic disconnections. This review highlights recent advances in Pd-catalyzed enantioselective C–H functionalization reactions with an emphasis on the catalytic pathways, types of chiral ligands, and chirality.

Highlights

Enantioselective C–H functionalization has emerged as a powerful and straightforward strategy to construct chiral molecules.

Compared with other transition-metal catalysts, palladium is particularly attractive as a catalyst for enantioselective C–H functionalization due to its high reactivity, incredible versatility, and good functional group tolerance.

The discovery of novel chiral ligands with high catalytic activity, simple structure, and modular synthesis would offer exciting opportunities for enantioselective C–H functionalization.

Different catalytic cycles of Pd-catalyzed enantioselective C–H activation

Recently, Pd-catalyzed enantioselective **C–H activation** (see Glossary) has gained momentum as an efficient and straightforward strategy to streamline the synthesis of enantiomerically enriched molecules [1–6]. In general, Pd-catalyzed asymmetric C–H activation can be categorized into four fundamentally different catalytic cycles based on the change of oxidation states of the palladium catalyst [1–6]: (i) The Pd(0)/Pd(II) catalytic cycle starts with the **oxidative addition** of the Pd(0) catalyst to organohalides (or pseudohalides) followed by C–H activation via a **concerted metalation–deprotonation (CMD)** [7,8] mechanism to generate the Pd(II) intermediate. **Reductive elimination** produces the products and regenerates the Pd(0) catalyst (Figure 1A); (ii) The Pd(II)/Pd(0) catalytic cycle begins with CMD-type C–H cleavage to form a Pd(II) intermediate, which undergoes **transmetalation** with an organometallic reagent and subsequent reductive elimination to give the product and a Pd(0) species. The catalytic cycle is closed by the oxidation of Pd(0) by an external oxidant to regenerate the active Pd(II) catalyst. Alternatively, the Pd(II) intermediate resulting from C–H activation could undergo migratory insertion with an olefin coupling partner, **β–H elimination**, to afford the product and close the catalytic cycle by the oxidation of Pd(0) (Figure 1B); (iii) The Pd(II)/Pd(IV) catalytic cycle involves the generation of the Pd(IV) intermediate by oxidative addition after the C–H activation. Reductive elimination affords the products and finishes the catalytic cycle (Figure 1C); (iv) Although rare, a redox-neutral Pd(II) mechanism is operative either via migration insertion followed by β–Y elimination or in a rare example via an electrophilic Pd–C bond cleavage (Figure 1D).

Chiral ligands can not only fine-tune the steric and electronic environment of the palladium catalyst to enhance the reactivity, but can also define the chiral environment of the catalyst to realize the synthesis of enantiopure products. Generally, different types of chiral ligands are needed for different catalytic cycles. Therefore, the design and development of novel chiral ligands with high catalytic activity, simple structure, and convenient synthesis to enable precise stereocontrol in a wide variety of reactions have always been a challenging scientific problem and direction for catalytic asymmetric synthesis. In the following sections, we discuss recent advancements in Pd-catalyzed enantioselective C–H functionalization reactions with the assistance of chiral ligands, covering asymmetric reactions proceeding through both enantiocontrolled C–H cleavage to generate chiral organopalladium complexes and enantiocontrolled functionalization of achiral

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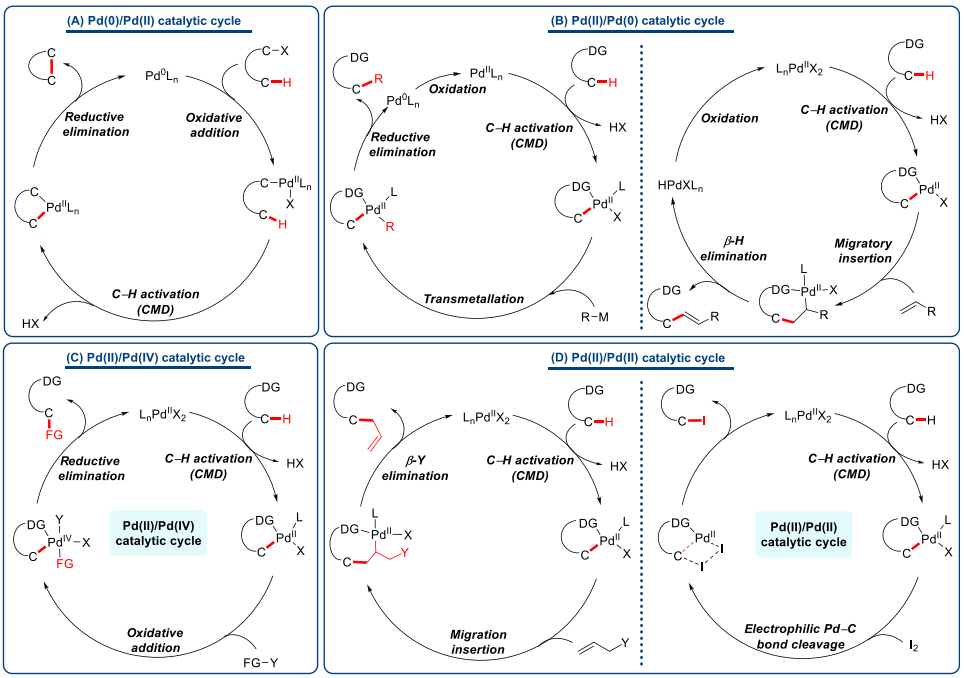


Figure 1. Different catalytic cycles of palladium-catalyzed C–H functionalization. (A) Pd(0)/Pd(II) catalytic cycle; (B) Pd(II)/Pd(0) catalytic cycle; (C) Pd(II)/Pd(IV) catalytic cycle; and (D) Pd(II)/Pd(II) catalytic cycle. Abbreviation: CMD, concerted metalation–deprotonation.

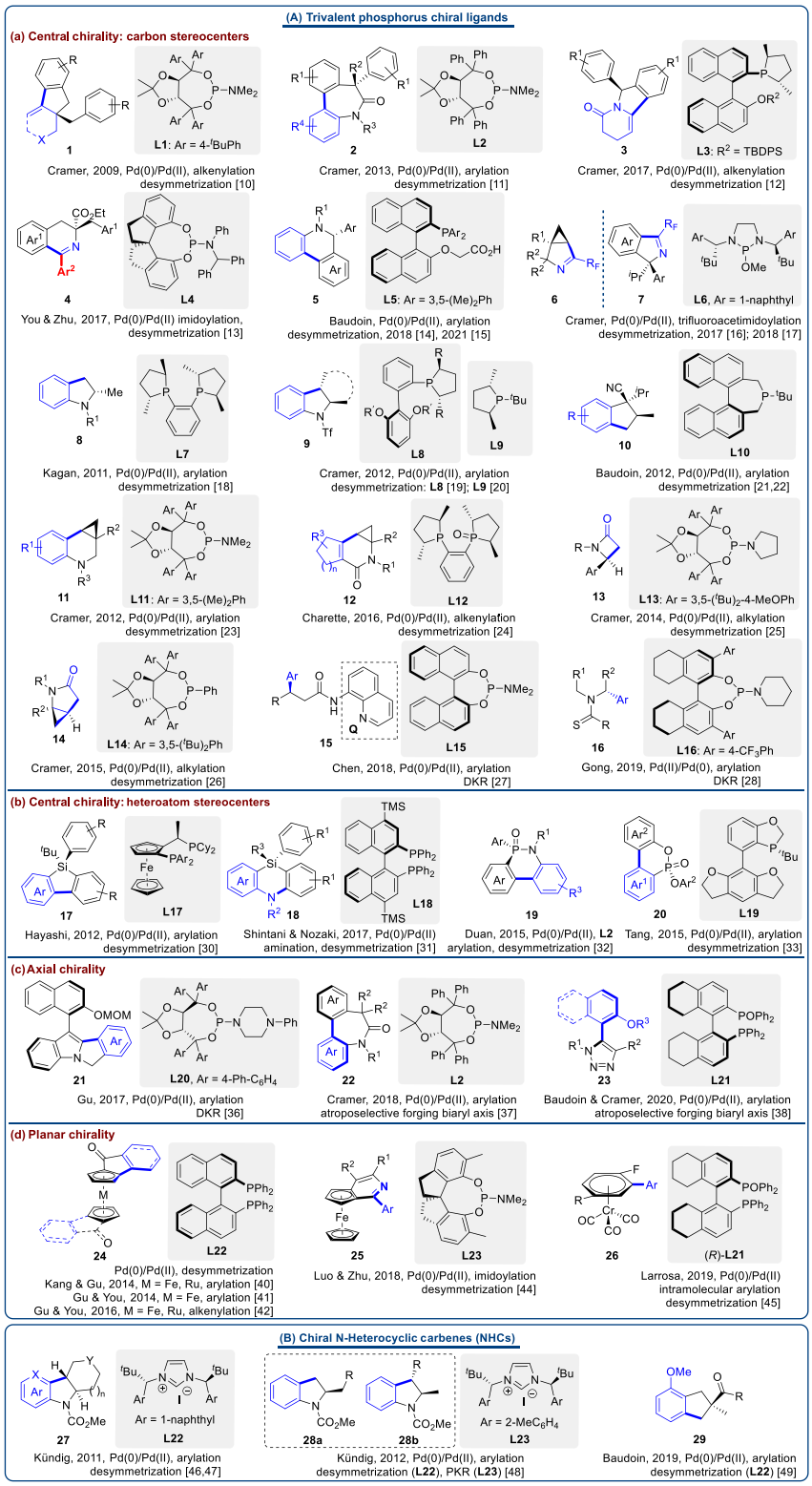
Glossary

C–H activation: the process of converting the carbon–hydrogen bond into a weaker carbon–metal bond.
Concerted metalation–deprotonation (CMD): the metal/base-promoted C–H bond cleavage that occurs by a simultaneous metalation and deprotonation processes.
β–H elimination: the process by which an alkyl group that is bonded to a metal center and has a hydrogen atom attached to the metal center can be converted into an alkene and a metal hydride.
Oxidative addition: the reverse of reductive elimination. A process by which a metal inserts into a covalent bond and formally increases its oxidation state by two.
Reductive elimination: an elementary organometallic step in which a new covalent bond is formed between two ligands, and the metal formally decreases its oxidation state by two.
Transmetalation: transfer of ligands from one metal center to another.

organopalladium intermediates. In this context, Pd-catalyzed asymmetric allylic C–H functionalization reactions proceeding through [(π-allyl)Pd] intermediates will not be included [9]. This review was classified by the types of chiral ligands used, which fall into the aforementioned four kinds of catalytic cycles.

Trivalent phosphorus chiral ligands

Trivalent phosphorus ligands have shown excellent performance in modern Pd(0)-catalyzed cross-coupling reactions. Recently, the great success of these ligands has been exemplified for its wide applications in inducing Pd(0)-catalyzed asymmetric C–H functionalization reactions (Figure 2A). A pioneering work of intramolecular C(sp^2)–H alkenylation to create quaternary stereocenters by the use of bulky phosphoramidite **L1** as ligand was demonstrated by Albicker and Cramer [10]. They subsequently reported impressive examples via intramolecular desymmetrizing C–H functionalization to construct several bioactive scaffolds [11,12]. In 2017, Zhu *et al.* elegantly demonstrated an efficient carbopalladation of the isocyanide group followed by an intramolecular desymmetrizing C(sp^2)–H arylation reaction using a SPINOL-derived phosphoramidite ligand **L4** [13]. A novel chiral bifunctional ligand based on a binaphthyl scaffold incorporating both a phosphine and a carboxylic acid moiety (**L5**) was developed by Baudoin and coworkers, which afforded high efficiency and enantioselectivity for desymmetrizing C(sp^2)–H arylation, leading to the formation of chiral 5,6-dihydrophenanthridines [14]. Recently, they have also achieved the synthesis of chiral fluoradenes and other warped molecules using this novel type of chiral bifunctional ligands [15]. Diazaphospholidines, a class of chiral ligands structurally related to *N*-heterocyclic carbenes (NHCs), have also been recognized as efficient ligands for asymmetric C–H activation, as demonstrated by Cramer in Pd(0)-catalyzed enantioselective cyclopropyl [16] and aryl [17] C–H trifluoroacetimidoylation with **L6**. Pd(0)-catalyzed asymmetric



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C(sp^3)–H activation with chiral phosphorous-containing chiral ligands has also emerged as a powerful strategy to access enantioenriched products. The groups of Kagan and Cramer independently demonstrated the efficient synthesis of chiral indoline scaffolds via intramolecular desymmetrizing methyl C(sp^3)–H arylations with bisphosphine (*R,R*)-Me-DUPhos (**L7**) [18], monophosphine SagePhos (**L8**) [19], or C_2-symmetric phospholane (**L9**) [20], respectively. Baudoin and coworkers also reported the synthesis of fused cyclopentanes via enantioselective methyl C(sp^3)–H arylation using *tert*-butyl-substituted BINEPINE **L10** [21]. The reaction was expanded to arylation of secondary C(sp^3)–H bonds on a cyclic system using the bench-stable phosphonium tetrafluoroborate salts of Binepines [22]. Asymmetric synthesis of chiral cyclopropanes via enantioselective C–H functionalization has also been achieved. The Cramer group developed an intramolecular C(sp^3)–H arylation of cyclopropyl methylene C(sp^3)–H bonds using TADDOL-derived phosphoramidite **L11** as ligand [23]. Ladd and Charette reported a Pd(0)-catalyzed enantioselective intramolecular C(sp^3)–H alkenylation of cyclopropanes using a bisphosphine monoxide ligand, namely, BozPHOS (**L12**) [24]. Chiral lactams are highly important scaffolds in bioactive natural products and pharmaceuticals. Uncommon disconnections were disclosed by the Cramer group through desymmetrizing alkylation of benzylic C–H bonds using TADDOL-derived phosphoramidite **L13** and cyclopropyl C–H bonds using TADDOL-derived monophosphine **L14** for the highly efficient synthesis of chiral β-lactams [25] and γ-lactams [26], respectively. In 2018, Chen and coworkers reported a protocol for Pd-catalyzed enantioselective benzylic C(sp^3)–H arylation directed by 8-aminoquinoline with BINOL-derived phosphoramidite **L15** [27]. Notably, the Gong group developed an unusual asymmetric thioamide-directed C(sp^3)–H arylation with a hybrid chiral palladium catalyst consisting of a chiral phosphoramidite **L16** and an anionic chiral Co(III) complex via the Pd(II)/Pd(0) catalytic cycle [28]. Asymmetric C–H functionalization strategy has also enabled the efficient synthesis of heteroatom-stereogenic compounds [29]. In 2012, the Hayashi group reported the synthesis of silicon-stereogenic dibenzosiloles through a Pd(0)-catalyzed enantioselective C–H arylation of prochiral 2-(arylsilyl)aryltriflates by employing Josiphos-type ligand (R,S_p)-**L17** [30]. Shintani and Nozaki reported an enantioselective 1,5-palladium migration/amination sequence to synthesize Si-stereogenic 5,10-dihydrophenazasilines using TMS (trimethylsilyl)-substituted (*R*)-BINAP (**L18**) [31]. By applying intramolecular asymmetric C(sp^2)–H arylation, Duan successfully developed a protocol for the synthesis of P-chiral phosphinic amides using TADDOL-derived phosphoramidite **L2** [32]. AntPhos-type ligand **L19**, an interesting type of phosphine ligands with a P-stereogenic benzooxaphosphole moiety, was used as an efficient ligand to enable the desymmetrizing C(sp^2)–H arylation to access various P-stereogenic biaryl phosphonates [33].

Enantioselective C–H activation has emerged as a powerful strategy to construct atropoisomeric compounds [34,35]. In 2017, Gu and coworkers reported the enantioselective synthesis of indole-based atropisomers via Pd-catalyzed intramolecular enantioselective C–H arylation via dynamic kinetic resolution (DKR) with a modified TADDOL-derived phosphoramidite **L20** [36]. A conceptually different approach via atroposelective C–H arylation to forge the biaryl axes was developed by the Cramer group with phosphoramidite **L2** [37]. Recently, Baudoin and Cramer reported an efficient access to axially chiral (hetero)biaryls by constructing the stereogenic axis via atroposelective C–H arylation employing H_8-BINAPO (**L21**) [38].

The synthesis of planar chiral molecules via asymmetric C–H activation has also attracted great attention [39]. Pd(0)-catalyzed enantioselective intramolecular desymmetrizing C–H functionalizations

Figure 2. (A) Trivalent phosphorus chiral ligands: (a) Central chirality: carbon stereocenters; (b) Central chirality: heteroatom stereocenters; (c) Axial chirality; and (d) Planar chirality. (B) Chiral *N*-heterocyclic carbenes. See [10–28,30–33,36–38,40–42,44–49]. Abbreviations: DKR, dynamic kinetic resolution; PKR, parallel kinetic resolution.

were developed to access planar chiral ferrocenes with readily available BINAP ligand (**L22**) by Kang and Gu [40], Gu and You [41,42]. This intramolecular desymmetrization strategy was successfully extended to the synthesis of planar chiral benzothiophene-fused ferrocenes with (*R*)-SEGPHOS by Duan [43]. Luo and Zhu reported a Pd(0)-catalyzed enantioselective isocyanide insertion/desymmetric C–H imidoylation with chiral SPINOL-derived phosphoramidite (**L23**) [44]. The Larrosa group disclosed the first intermolecular enantioselective C–H arylation of metallocenes using (*R*)-**L21** as ligand [45].

Chiral *N*-heterocyclic carbenes

Chiral NHC ligands have also been applied to Pd(0)-catalyzed asymmetric C–H activation, as pioneered by Kündig and coworkers in the synthesis of enantio-enriched fused indolines via desymmetrizing arylation of cyclic methylene C–H bonds using a C_2-symmetric NHC (**L22**) [46,47] (Figure 2B). Later, they further disclosed that NHCs (**L22** or **L23**) could be applied to parallel kinetic resolution (KR) of racemic substrates [48]. Recently, Baudoin reported the desymmetrization of *gem*-dimethyl group by enantioselective C(sp^3)–H arylation employing NHC (**L22**) as ligand, which was used as the key step in the enantioselective synthesis of (nor) illudalane sesquiterpenes [49].

Mono-*N*-protected amino acid ligands

Pd(II)-catalyzed enantioselective C–H activation has been a longstanding challenge due to the lack of appropriate chiral ligands. Trivalent phosphorus chiral ligands that are commonly used in Pd(0) chemistry are generally incompatible with the oxidative conditions for Pd(II)-catalyzed C–H activation. Therefore, the design of modular, easily accessible, and oxidation-resistant chiral ligands that can simultaneously modulate the reactivity and effectively control the stereoselectivity is at the forefront of C–H activation. The major breakthrough was made by the Yu group (Figure 3). In 2008, they first disclosed that mono-*N*-protected amino acid (MPAA) ligands could promote the Pd(II)-catalyzed asymmetric alkylation of prochiral C(sp^2)–H and C(sp^3)–H bonds directed by pyridine, with (–)-Men-Leu-OH (**L28**) as the optimal one [50]. Subsequent mechanistic studies led to the exciting finding that the MPAA ligands bind to palladium in a bidentate mode and the *N*-acyl group acts as an internal base in the CMD step [51]. Since this seminal work, MPAA ligands have been widely applied to Pd(II)-catalyzed enantioselective C–H functionalization of a range of substrates with different directing groups (DGs). In 2010, the Yu group reported a carboxylate-directed enantioselective C(sp^2)–H olefination using Boc-Ile-OH (**L25**) as chiral ligand [52]. In addition to the cross-coupling with organoborons and oxidative Heck-type olefination reactions through the Pd(II)/Pd(0) catalytic cycle, MPAA ligands are also viable to asymmetric C–H activation reactions proceeding through the Pd(II)/Pd(IV) catalytic cycle. In 2013, Wang and Yu reported the first intramolecular asymmetric C(sp^2)–H lactonization via a Pd(II)/Pd(IV) catalytic cycle using Boc-Ile-OH (**L25**) as chiral ligand [53]. Yu and coworkers reported the first Pd-catalyzed enantioselective C(sp^2)–H iodination reaction via desymmetrization of diaryltriflamides using Bz-Leu-OH (**L26**) [54]. Interestingly, computational studies showed that this catalytic system may preferentially proceed via a rare Pd(II) redox-neutral electrophilic cleavage pathway [55]. Shortly after, Yu and coworkers reported a Pd(II)-catalyzed enantioselective C(sp^2)–H iodination of benzylic amines via KR [56] using the same ligand. In contrast to the desymmetric C–H iodination, computational studies by Dang and co-workers proposed that this reaction may proceed through a Pd(II)/Pd(IV) catalytic cycle [57]. They successfully expanded the KR of α-hydroxy and α-amino phenylacetic acids via Pd(II)-catalyzed enantioselective C(sp^2)–H olefination using Boc-Thr(Bz)-OH (**L27**) [58]. MPAA-type ligands are also efficient for Pd(II)-catalyzed asymmetric functionalization of cyclopropyl C(sp^3)–H bonds. The Yu group reported the first Pd(II)-catalyzed enantioselective C(sp^3)–H functionalization of cyclopropanes using a tailor-made MPAA ligand **L28** [59]. Asymmetric C(sp^3)–H functionalization of

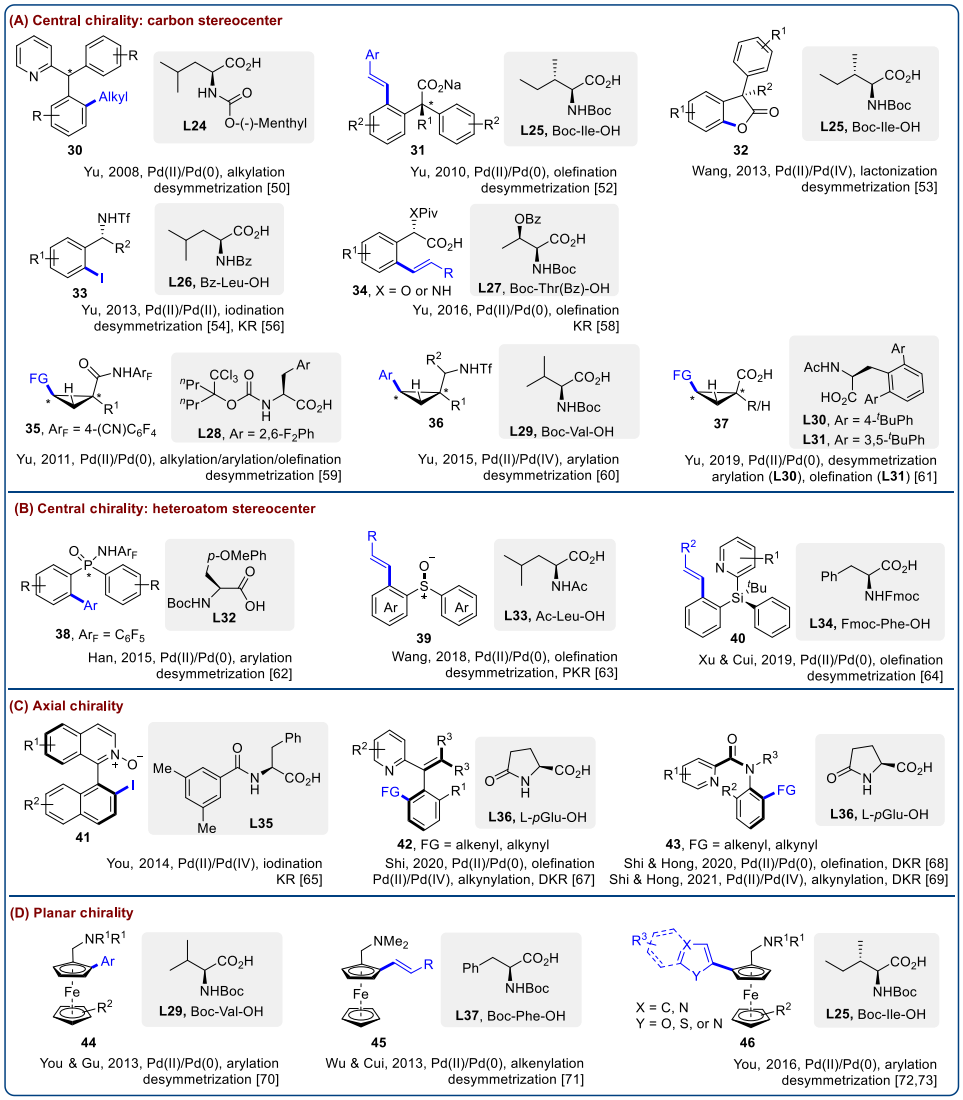

Figure 3. Mono-*N*-protected amino acid ligands: (A) central chirality: carbon stereocenters; (B) central chirality: heteroatom stereocenters; (C) axial chirality; and (D) planar chirality. See [50,52–54,56,58–65,67–73]. Abbreviations: DKR, dynamic kinetic resolution; KR, kinetic resolution; PKR, parallel kinetic resolution.

cyclopropylmethylamines [60] and cyclopropanecarboxylic acids [61] has also been achieved using MPAA ligands (**L29**–**L31**) by the same group. Inspired by Yu's seminal works on the Pd(II)/MPAA system, Han and coworkers achieved the first construction of P-stereogenic centers through Pd(II)-catalyzed desymmetric C–H arylation of diarylphosphinamides with the MPAA ligand **L32** (Figure 3B) [62]. The Wang group reported the first synthesis of chiral sulfoxides via Pd(II)-catalyzed asymmetric C(sp^2)–H olefination through desymmetrization and parallel KR using Ac-Leu-OH (**L33**) as ligand [63]. The synthesis of silicon-stereogenic silanes via desymmetric C(sp^2)–H olefination was reported by Xu and Cui using Fmoc-Phe-OH (**L34**) as ligand [64].

Enantioselective synthesis of axially chiral compounds via C–H activation remained an unresolved challenge until the pioneering work by You (Figure 3C) [65]. In 2014, You and coworkers reported the first synthesis of axially chiral biaryls via Pd-catalyzed C(sp^2)–H iodination/KR with MPAA **L35** [65]. The Yang group expanded this protocol to the enantioselective C–H olefination of biaryl phosphines using Boc-Val-OH (**L29**) as chiral ligand [66]. The asymmetric synthesis of axially chiral styrenes with an open-chained alkene, which was much more challenging due to the lower rotational barrier, was first reported by Shi and coworkers using a Pd(II)/L-*p*Glu-OH (**L36**) catalytic system [67]. The synthesis of atropisomeric anilides possessing restricted rotation around an N-aryl chiral axis via asymmetric C–H bond functionalization remains rare, largely because atropisomeric anilides are conformationally more flexible than their biaryl cousins. Recently, the Shi group successfully expanded the Pd(II)/L-*p*Glu-OH (**L36**) catalytic system to the highly efficient synthesis of atropisomeric anilides via atroposelective C–H olefination/alkynylation [68,69].

The Pd(II)/MPAA catalytic systems could also be used for the construction of planar chiral ferrocenes (Figure 3D). A major breakthrough was achieved by You and Gu for Pd(II)-catalyzed enantioselective C–H arylation of aminomethylferrocenes with commercially available Boc-Val-OH (**L29**) in 2013 [70]. Wu and Cui independently reported an enantioselective C–H olefination of *N*,*N*-dimethylaminomethylferrocene with Boc-Phe-OH (**L37**) [71]. You and coworkers further achieved an enantioselective twofold C–H oxidative arylation between aminomethylferrocenes and heteroarenes with Boc-Ile-OH (**L25**) [72,73].

In short, the MPAA ligands arguably have been recognized as the most widely used chiral ligands in Pd(II)-catalyzed enantioselective C–H functionalization with a monodentate DG in various different catalytic cycles, such as Pd(II)/Pd(0), Pd(II)/Pd(IV), and Pd(II)/Pd(II).

Bifunctional ligands based on MPAAs

The discovery and development of bifunctional MPAA ligands make great strides toward accelerating and improving the selectivity of Pd-catalyzed C–H functionalization. Mechanistic studies have identified the key structural elements of MPAAs that influence C–H activation, specifically the bidentate coordination of the carboxylate and amide and the active participation of the *N*-acyl group in C–H cleavage [51]. Inspired by these insights, a variety of MPAA-related next-generation bifunctional ligands have been designed by Yu and coworkers, including mono-*N*-protected α-amino-*O*-methylhydroxamic acid (MPAHA), acetyl-protected aminoethyl quinoline (APAQ), *N*-acyl-protected aminomethyl oxazoline (APAO), mono-*N*-protected aminoethyl amine (MPAAM), *N*-acyl-protected aminoethyl sulfoxide (APASulfoxide), and *N*-acyl-protected aminoethyl thioether (APAThio; Figure 4) [51]. In 2014, MPAHA ligand (**L38**) was first synthesized to achieve Pd(II)-catalyzed desymmetrizing arylation of cyclobutyl C(sp^3)–H bonds with arylboron reagents by Yu and coworkers [74] (Figure 4A). The Pd(II)-catalyzed enantioselective C(sp^2)–H arylation of nosyl-protected diarylmethylamines via desymmetrization using MPAHA ligand (**L39**) was reported by the same group [75]. They further achieved the enantioselective C–H arylation/KR of benzylamines using the MPAHA ligand Boc-Phe-NHOMe (**L40**) [76]. Wang reported a Pd(II)-catalyzed asymmetric C(sp^2)–H carbonylation with carbon monoxide using MPAHA ligand (**L41**) [77]. Enantioselective differentiation of prochiral C–H bonds on a single methylene carbon via asymmetric metal insertion is a long-term challenge. A breakthrough was made by the Yu group by the design of a novel type of APAQ chiral ligands in 2016 [78] (Figure 4B). They reported a Pd(II)-catalyzed enantioselective arylation of unbiased methylene C(sp^3)–H bonds of aliphatic amides using APAQ ligand (**L42**) [78]. The utility of this kind APAQ ligand was further demonstrated by the enantioselective C(sp^3)–H arylation of methylene groups in cycloalkanes [79]. In 2017, the Yu group reported the first example of β-C(sp^3)–H arylation, alkenylation, and alkynylation of isobutyric amides via desymmetrization of *gem*-

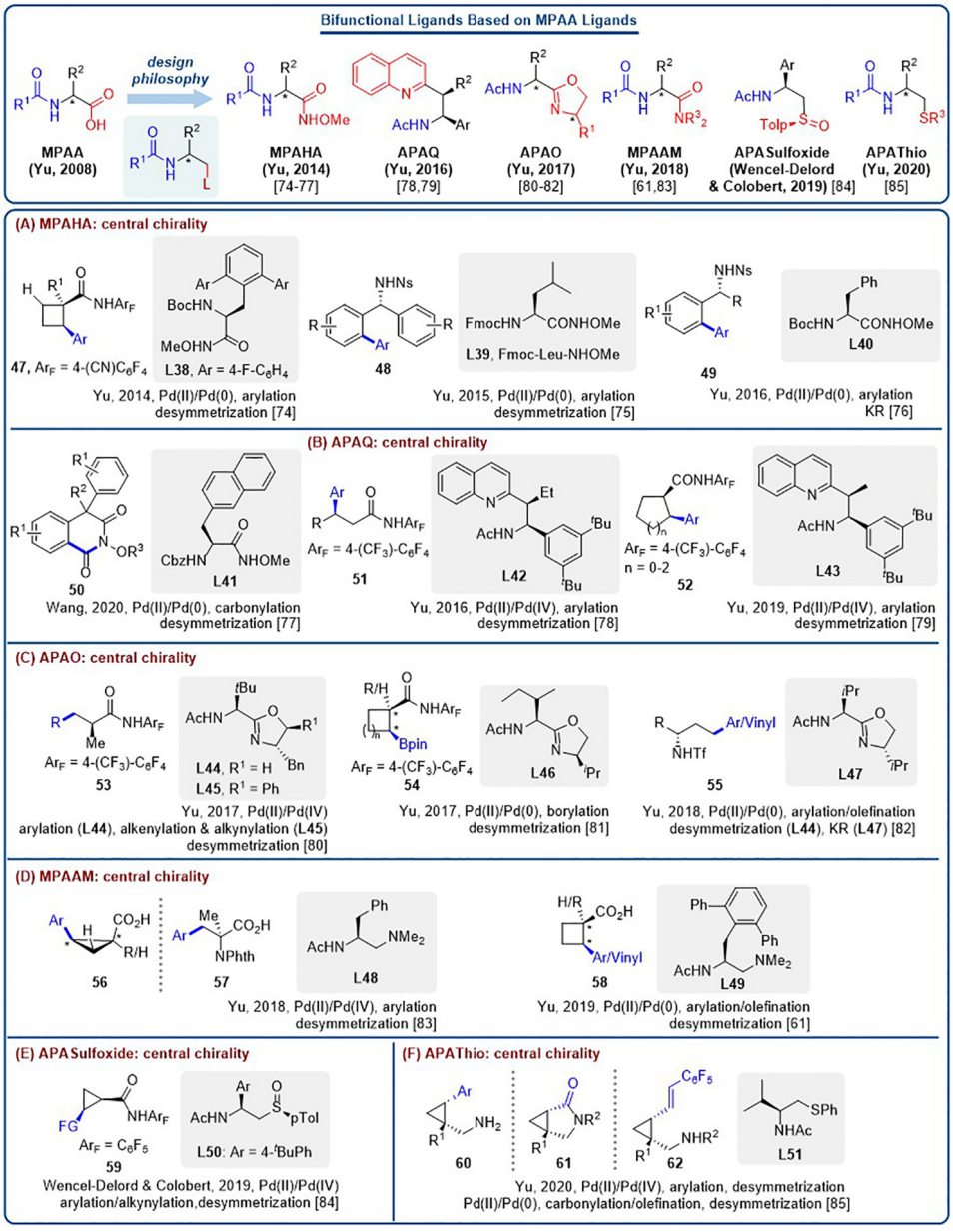

Figure 4. Bifunctional ligands based on mono-*N*-protected amino acid (MPAA) ligands: (A) α-amino-*O*-methylhydroxamic acid (MPAHA): central chirality; (B) *N*-acetyl-protected aminoethyl quinoline (APAQ): central chirality; (C) *N*-acyl-protected aminomethyl oxazoline (APAO): central chirality; (D) mono-*N*-protected aminoethyl amine (MPAAM): central chirality; (E) *N*-acyl-protected aminoethyl sulfoxide (APASulfoxide): central chirality; and (F) *N*-acyl-protected aminoethyl thioether (APAThio): central chirality. See [61,74–85].

dimethyl C(sp^3)–H bonds with APAO ligands (**L44**, **L45**) [80] (Figure 4C). APAO ligands could also be applied to the asymmetric β-C(sp^3)–H borylation of cyclobutanecarboxylic acid derivatives [81] and γ-C(sp^3)–H arylation and alkenylation of alkylamines [82]. In 2018, Yu and

coworkers reported a Pd-catalyzed enantioselective C-(sp^3)–H arylation of cyclopropane carboxylic and 2-aminoisobutyric acids by employing a novel MPAAM ligand (**L48**) [83] (Figure 4D). They subsequently developed a Pd(II)-catalyzed enantioselective C(sp^3)–H cross-coupling of free cyclobutane carboxylic acids with organoborons using MPAAM ligand (**L49**) [61]. In 2019, Wencel-Delord and Colobert elegantly designed an easily accessible APASulfoxide ligand (**L50**), which enabled the Pd-catalyzed enantioselective C(sp^3)–H arylation of cyclopropane carboxylamides with aryl iodides [84] (Figure 4E). Recently, a novel APAThio ligand **L59** was developed by Yu and coworkers, which afforded high efficiency and enantioselectivity for a desymmetrizing C(sp^3)–H arylation, carbonylation, and olefination of free aliphatic cyclopropylmethylamines [85] (Figure 4F).

Free amino acids and the corresponding amides as transient chiral auxiliaries

Chelation assistance has shown remarkably efficiency and chemoselectivity in metal-catalyzed C–H activation reactions; however, the installation and removal of DGs are major drawbacks for their synthetic applications. The major breakthrough was made by the Yu group in 2016. They reported the first enantioselective C(sp^3)–H arylation of 2-alkyl benzaldehydes using commercially available L-*tert*-leucine (Tle, **L52**) as a catalytic transient chiral auxiliary [86] (Figure 5A). This strategy also worked for enantioselective C(sp^3)–H fluorination of 2-alkyl benzaldehydes by using a bulky amino amide (**L53**) as transient chiral auxiliary [87]. In the proposed stereocontrol model, steric repulsion between the side chain of transient chiral auxiliary and the R^2 group of the 2-alkyl benzaldehydes forced them to adopt a *trans*-conformation in the transition structure. As an elegant extension of this novel strategy, Yu and coworkers recently reported a Pd(II)-catalyzed enantioselective β-C(sp^3)–H arylation of cyclobutyl ketones with D-valine (**L54**) [88].

Inspired by Yu's innovative works on the construction of central chirality with transient directing strategy, the Shi group achieved the construction of axial chirality using Tle (**L52**) as a catalytic transient chiral auxiliary (Figure 5B). The synthesis of chiral biaryl aldehydes via Pd(II)-atroposelective C–H olefination [89], alkynylation [90], allylation [91], naphthylation [92], and C–H/C–C cleavage [93] has been achieved by Shi and coworkers using Tle (**L52**). This strategy has also enabled the efficient, asymmetric synthesis of several natural products, including TAN-1085 [94], (+)-isoschizandrin, and (+)-steganone [90]. This strategy was also amendable to the efficient

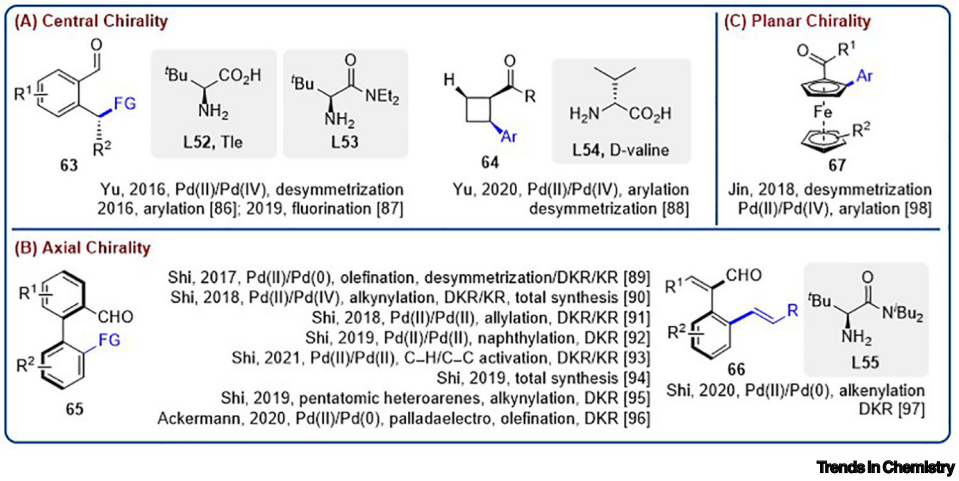

Figure 5. Free amino acids and the corresponding amides as transient chiral auxiliaries: (A) central chirality; (B) axial chirality; and (C) planar chirality. See [86–98]. Abbreviation: DKR, dynamic kinetic resolution.

synthesis of enantioenriched pentatomic biaryls with lower rotational barriers [95]. Ackermann and coworkers unraveled the first palladium and electro-catalyzed atroposelective C–H olefination with the aid of Tle (**L52**) [96]. The Shi group also achieved the asymmetric synthesis of more challenging axially chiral styrenes via atroposelective C–H olefination by the use of a bulky amino amide (**L55**) as the catalytic transient chiral auxiliary [97]. The transient chiral auxiliary strategy also enabled the construction of planar chiral ferrocenes by Jin and coworkers using Tle (**L52**) (Figure 5C) [98].

Chiral phosphoric acids

Recently, the use of chiral phosphoric acids (CPAs) as ligands to enable enantioselective C–H activation with palladium catalysts has brought new opportunities to asymmetric C–H functionalization. In 2015, Duan and coworkers reported the first example of using BINOL-derived phosphoric acid (**L56**) and amide (**L57**) as chiral ligands, which allowed the Pd(II)-catalyzed arylation of benzylic methylene C–H bonds in modest enantioselectivity directed by a strongly coordinating bidentate 8-aminoquinoline auxiliary [99] (Figure 6A). Chen and coworkers further expanded this protocol to the enantioselective arylation of benzylic methylene C–H bonds

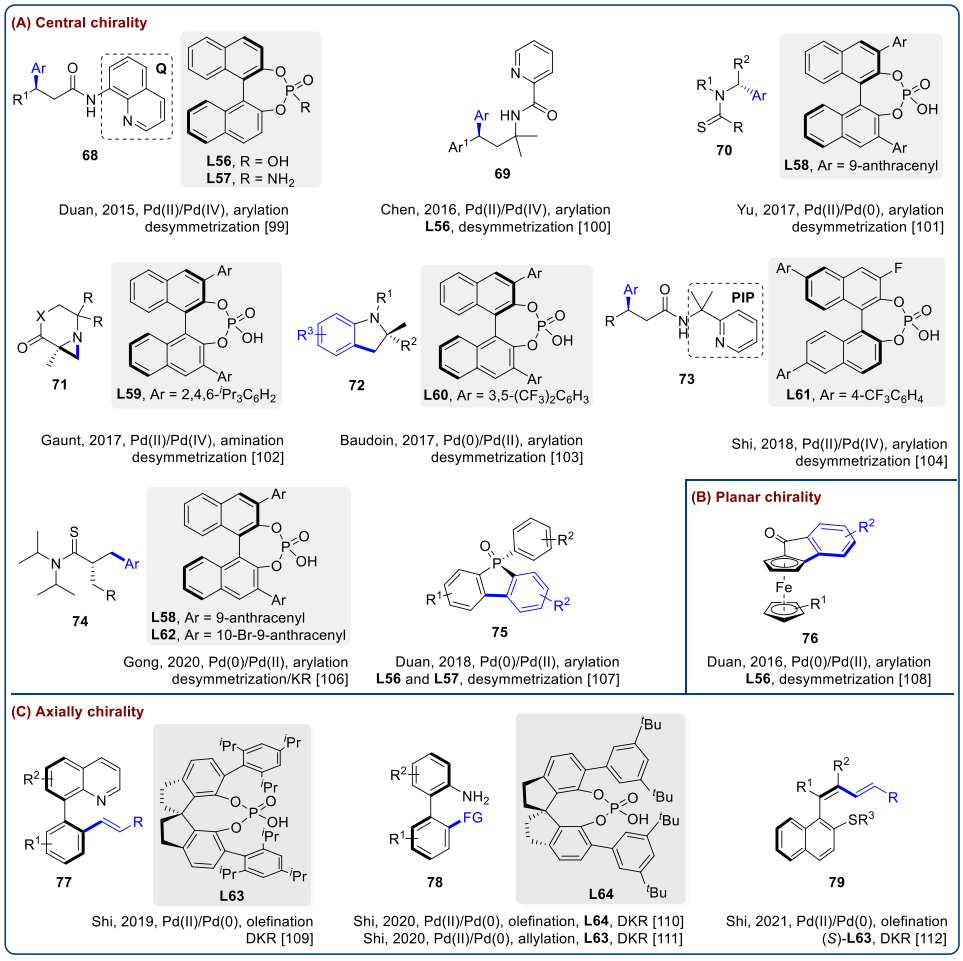

Figure 6. Chiral phosphoric acids: (A) central chirality; (B) planar chirality; and (C) axially chirality. Abbreviations: DKR, dynamic kinetic resolution; KR, kinetic resolution. See [99–104,106–112].

directed by a picolinamide auxiliary [100]. The Yu group demonstrated an enantioselective α-C(sp^3)–H arylation of amines catalyzed by the Pd(II)/CPA (**L58**) catalytic system using a thioamide DG [101]. Gaunt and coworkers developed an elegant Pd(II)-catalyzed enantioselective intramolecular C(sp^3)–H amination to synthesize chiral aziridines using a sterically bulky CPA ligand (**L59**) [102]. Baudoin *et al.* [103] reported the first efficient Pd(0)-catalyzed asymmetric C(sp^3)–H arylation using a CPA ligand (**L60**) and an achiral phosphine ligand via a Pd(0)/Pd(II) catalytic cycle. Enantioselective functionalization of unbiased methylene C–H bonds by stereo-controlled C–H metalation has been a long-term challenge. The Shi group reported a highly efficient Pd(II)-catalyzed enantioselective arylation of unbiased methylene C(sp^3)–H bonds by the cooperative effect between their newly developed 2-pyridinylisopropyl (PIP) bidentate auxiliary and a non-C_2-symmetric CPA ligand (**L61**) [104]. An intermolecular version of this protocol has been disclosed by the same group [105]. Gong and coworkers reported an enantioselective β-C(sp^3)–H arylation of thioamides with excellent enantioselectivities using CPA ligands (**L58** or **L62**) [106]. Duan and coworkers reported the synthesis of P-stereogenic dibenzophospholes via $Pd(PCy_3)_2$-catalyzed asymmetric intramolecular C–H arylation using CPA (**L56**) and amide (**L57**) [107]. The enantioselective synthesis of planar chiral ferrocenes via Pd(0)-catalyzed asymmetric intramolecular C(sp^2)–H arylation using CPA ligand (**L56**) and achiral phosphine ligand was described by the Duan group in 2016 [108] (Figure 6B).

Chiral spiro phosphoric acids have proven to be a type of competent chiral ligands in palladium-catalyzed asymmetric C–H activation by the Shi group. In 2019, they first demonstrated the synthesis of axially chiral quinoline atropisomers by Pd(II)-catalyzed enantioselective C–H olefination

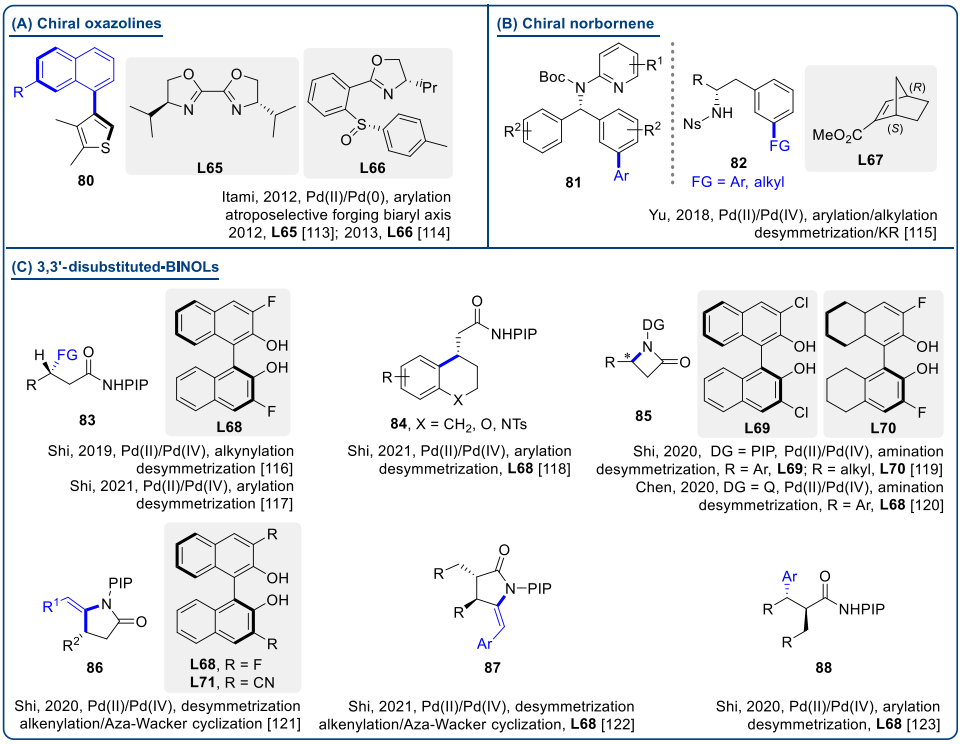

Figure 7. Other chiral ligands: (A) chiral oxazolines; (B) chiral norbornene; and (C) 3,3′-disubsituted-BINOLs. See also [113–123].

using a sterically bulky spiro phosphoric acid ligand (**L63**) [109] (Figure 6C). This protocol was successfully applied to the atroposelective C–H olefination and allylation of biaryl-2-amines using **L64** and **L63**, respectively [110,111]. Very recently, they developed a new approach to access the axially chiral styrenes with a conjugated 1,3-diene scaffold by using *(S)*-**L63** as an efficient chiral ligand [112].

Other chiral ligands: chiral oxazolines, chiral norbornene, and 3,3′-disubsituted-BINOLs

Several other types of chiral ligands have also been developed for Pd-catalyzed enantioselective C–H activation (Figure 7). The Itami group reported the synthesis of hindered biaryls via C–H coupling of sterically hindered heteroarenes and arylboronic acids. The use of 2,2′-bis(2-oxazoline) (biox, **L65**) and sulfoxide-oxazoline (sox, **L66**) as chiral ligand led to moderate enantioselectivity [**L65**, 41-72% enantiomeric excess (ee); **L66**, 61% ee] [113,114].

Although various catalytic systems have been developed, the reported methods were typically limited to the formation of five- or six-membered palladacycles. Enantioselective C–H functionalization through a conformationally more flexible palladacycle remains exclusive, largely because the palladium insertion occurs far away from the chiral center to be created. In 2018, Yu and coworkers realized the first example of remote enantioselective C–H activation reactions by relaying *ortho*-C–H activation to remote *meta*-position using palladium and chiral norbornene (**L67**) cooperative catalysis through desymmetrization/KR approach [115] (Figure 7B).

To address the challenge of enantioselective functionalization of unbiased methylene C(sp^3)–H bonds of linear systems, the Shi group has recently developed a novel type of chiral ligands, namely 3,3′-disubstituted BINOLs, which were readily available and highly tunable. These type of BINOL ligands have enabled the diverse functionalization of unbiased methylene C(sp^3)–H bonds with the combination of PIP DG (Figure 7C). In 2019, Shi and coworkers reported the first Pd(II)-catalyzed enantioselective alkynylation of unbiased methylene C(sp^3)–H bonds using 3,3′-F_2-BINOL (**L78**) as chiral ligand assisted by PIP DG [116]. This catalytic system was expanded to intermolecular and intramolecular enantioselective C–H arylation with aryl iodides [117,118]. The Shi and Chen groups independently demonstrated the efficient synthesis of chiral β-lactams via intramolecular C(sp^3)–H amination with the combination of bidentate DGs and 3,3′-disubstituted BINOLs (DG = PIP, **L69** and **L70**; DG = Q, **L68**) [119,120]. The Shi group further showcased that 3,3′-substituted BINOLs were enabling chiral ligands to promote enantioselective aliphatic methylene C(sp^3)–H alkenylation/Aza–Wacker reaction sequence to synthesize β-stereogenic γ-lactams [121,122]. The enantioselective desymmetrizing C–H activation of α-*gem*-dialkyl acyclic amides remains a huge challenge, because the availability of four chemically identical unbiased methylene C(sp^3)–H bonds and increased rotational freedoms of the acyclic systems added tremendous difficulties for chemocontrol and stereocontrol. Shi and coworkers recently developed a novel approach for highly efficient synthesis of acyclic aliphatic amides with α,β-contiguous stereogenic centers by desymmetric C–H arylation of *gem*-dialkyl C(sp^3)–H bonds using **L68** as chiral ligands and PIP as bidentate DG [123].

Concluding remarks

In this review, we have summarized recent developments in palladium-catalyzed enantioselective C–H functionalization reactions via different catalytic cycles for the construction of chiral compounds (Table 1). The flourish of this strategy has streamlined the construction of complex chiral molecules from simple feedstock in an atom- and step-economical manner. Despite these remarkable advances, several challenges still need to be addressed. For example, the discovery of novel types of ligands, which are readily available, easily tunable, and highly efficient to promote

Outstanding questions

Can palladium-catalyzed enantioselective C–H functionalization reactions be used to construct chiral skeletons (such as helically chiral compounds) that are currently difficult to obtain?

Is it possible to forge more challenging carbon–heteroatom bonds by palladium-catalyzed enantioselective C–H functionalization?

Can palladium-catalyzed enantioselective C–H functionalization reactions be widely used as key steps in the synthesis of natural products and drug molecules?

Can palladium-catalyzed enantioselective C–H functionalization be conducted in mild conditions and low catalyst loading?

Is it possible to create multiple stereogenic centers in a single transformation?

Table 1. Summary of chiral ligands, catalytic cycles, transformations, and the types of chirality

Chiral ligand	Catalytic cycle	Transformation	Chirality
Trivalent phosphorus	Pd(0)/Pd(II) ☑	■ Alkenylation [10,12,24,42]	Central chirality ☑
	Pd(II)/Pd(0) ☑	■ Arylation [11,14,15,18–23,27,28,30,32,33,36–38,40,41,45]	Axial chirality ☑
	Pd(II)/Pd(IV) ☒	■ Imidoylation [13,44]	Planar chirality
	Pd(II)/Pd(II) ☒	■ Trifluoroacetimidoylation [16,17]	Helical chirality
		■ Alkylation [25,26]	
		■ Amination [31]	
NHC	Pd(0)/Pd(II) ☑	■ Arylation [46–49]	Central chirality ☑
MPAA	Pd(0)/Pd(II) ☒	■ Alkylation [50,59]	Central chirality ☑
	Pd(II)/Pd(0) ☑	■ Olefination [52,58,59,61,63,64,67,68,71]	Axial chirality ☑
	Pd(II)/Pd(IV) ☑	■ Lactonization [53]	Planar chirality
	Pd(II)/Pd(II) ☑	■ Iodination [54,56,65]	Helical chirality
		■ Alkynylation [67,69]	
		■ Arylation [59–62,70,72,73]	
Bifunctional ligands based on MPAA	Pd(0)/Pd(II) ☒	■ Arylation [61,74,75,78,79,82–85]	Central chirality ☑
	Pd(II)/Pd(0) ☑	■ Carbonylation [77,85]	Axial chirality ☒
	Pd(II)/Pd(IV) ☑	■ Olefination [61,80,82,85]	Planar chirality
	Pd(II)/Pd(II) ☒	■ Alkynylation [80,84]	Helical chirality
		■ Borylation [81]	
Free amino acid and the corresponding amide	Pd(0)/Pd(II) ☒	■ Arylation [86,88,98]	Central chirality ☑
	Pd(II)/Pd(0) ☑	■ Fluorination [87]	Axial chirality ☑
	Pd(II)/Pd(IV) ☑ **Pd(II)/Pd(II) ☑**	■ Olefination [89,94,96,97] ■ Alkynylation [90,95]	Planar chirality Helical chirality
		■ Allylation [91]	
		■ Naphthylation [92]	
		■ C–H/C–C activation [93]	
CPA	Pd(0)/Pd(II) ☑	■ Arylation [99–101,103–108]	Central chirality ☑
	Pd(II)/Pd(0) ☑	■ Amination [102]	Axial chirality ☑
	Pd(II)/Pd(IV) ☑	■ Olefination [109,110,112]	Planar chirality
	Pd(II)/Pd(II) ☒	■ Allylation [111]	Helical chirality
Oxazoline	Pd(II)/Pd(0) ☑	■ Arylation [113,114]	Axial chirality ☑
Norbornene	Pd(II)/Pd(IV) ☑	■ Arylation and alkylation [115]	Central chirality ☑
3,3′-Disubstituted BINOLs	Pd(0)/Pd(II) ☒	■ Arylation [117,118,123]	Central chirality ☑
	Pd(II)/Pd(0) ☒	■ Alkynylation [116]	Axial chirality ☒
	Pd(II)/Pd(IV) ☑	■ Amination [119,120]	Planar chirality
	Pd(II)/Pd(II) ☒	■ Alkenylation/Aza–Wacker cyclization [121,122]	Helical chirality

both the reactivity and enantiocontrol, remains a key future objective (see Outstanding questions). Currently, the substrate scope for enantioselective C–H functionalization is still limited. It would be highly desirable to render this strategy to be more general for a broad range of densely functionalized substrates. In addition, Pd-catalyzed enantioselective C–H functionalization has been applied to the construction of chiral molecules bearing central, axial, and planar chirality, however, the construction of helically chiral compounds through this strategy remains elusive (Table 1).

Furthermore, as demonstrated earlier, current methods are largely limited to C–C bond formation, and the synthesis of chiral compounds through the formation of carbon–heteroatom bonds (e.g., C–O, C-N, and C–X) remains rare. Finally, it is extremely challenging to apply the enantioselective C–H functionalization strategy in natural product syntheses [90,94,124] and industrial application.

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Declaration of interests

No interests are declared.

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